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First International Symposium on Nonthermal Medical/Biological Treatments Using Electromagnetic Fields and Ionized Gases

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In order to provide a forum for the exchange of information and ideas in these emerging research and technology fields, the "First International Symposium on Nonthermal Medical/Biological Treatments Using Electromagnetic Fields and Ionized Gases" ("ElectroMed99," for short) was held on April 12-14, 1999 in Norfolk, Virginia. The Symposium was sponsored by the U.S. Air Force Office of Scientific Research, the National Science Foundation, IEEE Nuclear and Plasma Sciences Socity, the Bioelectromagnetics Society, Old Dominion University, the Eastern Virginia Medical School, and the College of William and Mary. One hundred and thirty-five scientists from twelve countries attended.

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SUMMARY

Breakthroughs in the generation of high power, submicrosecond, electromagnetic wave sources and in the generation of atmospheric pressure gas discharges have opened paths to new methods in biological decontamination, biological cell manipulation, medical diagnostics and therapy. In order to provide a forum for the exchange of information and ideas in these emerging research and technology fields, the "First International Symposium on Nonthermal Medical/Biological Treatments Using Electromagnetic Fields and Ionized Gases" ("ElectroMed99," for short) was held on April 12–14, 1999 in Norfolk, Virginia. The Symposium was sponsored by the U.S. Air Force Office of Scientific Research, the National Science Foundation, IEEE Nuclear and Plasma Sciences Society, the Bioelectromagnetics Society, Old Dominion University, the Eastern Virginia Medical School, and the College of William and Mary. One hundred and thirty-five scientists from twelve countries attended.

In order to introduce the audience (which consisted of engineers, physicists, biologists and clinicians) to these research areas, we had invited prominent scientists to give tutorials and reviews on the important research areas in nonthermal treatments and on the supporting plasma, pulsed power, and microwave technology. Eighteen invited talks were given in the first two days of the meeting, covering a range of topics from basic microbiology to pulsed power technology. Approximately sixty contributed papers were presented in a poster session. The largest research and development area represented in the poster session was bacterial decontamination using pulsed electric fields, UV radiation, and nonthermal plasmas. The second largest area dealt with basic studies and medical applications of pulsed electric fields. The relatively large number of papers on pulsed field generators, mainly presented by scientists from the former Soviet Union, provided the audience with a good overview of leading edge pulsed power systems.

In order to introduce this new, interdisciplinary research field to a wider scientific community, particularly to the engineering community, a special issue on this topic is being published in the IEEE Transactions of Plasma Science. The special issue which will appear in February of 2000 contains 33 contributions, 14 of them Invited Papers. As the first special issue on this topic, it is expected that it becomes a "classic" in the literature on nonthermal biological/medical treatments.

Success in this emerging, truly interdisciplinary, research field requires the cooperation of scientists with background in physics, engineering, chemistry, biology and medicine. Our attempt to bring scientists with such a diverse background together, and encourage them to share their knowledge and exchange their views has been considered by the overwhelming majority of the participating scientists as successful. The program committee, an international board of scientists, has already decided to hold a second symposium on this topic again in Norfolk in 2001, with Prof. Beebe from EVMS as chairman.

Documentation

Symposium

1. Letterhead
2. First Announcement
3. Second Announcement
4. Web-Page
5. Organizing and Program Committee
6. Agenda
7. Proceedings
8. Attendees' List
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9. Proposal
10. Announcement
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NONTHERMAL MEDICAL/BIOLOGICAL TREATMENTS USING ELECTROMAGNETIC FIELDS AND IONIZED GASES

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Abstract

The application of intense electrical pulses to biological cells causes changes in the permeability of the cell membranes. This effect, electroporation, is the basis of numerous medical, industrial and environmental applications. The development of nanosecond and even subnanosecond high power pulse generators and pulsed microwave sources promises to expand this range of nonthermal electric field – cell interactions from the cellular to the molecular level, with the potential for novel medical treatments. A research field which is mainly established in the FSU countries and in China deals with the biological effects of microwaves and millimeter waves. Extended scientific studies in this field may lead to novel therapeutic, health and safety applications. A second technological area, which has developed rapidly, is the generation of nonthermal, atmospheric pressure plasmas, with application in bacterial and chemical decontamination. In order to provide a forum for exchange of information and ideas the "First International Symposium on Nonthermal Medical/Biological Treatments Using Electromagnetic Fields and Ionized Gases" was held in April of 1999 in Norfolk, VA. The paper provides an overview of the state of these emerging research and technology fields based on the conference presentations, and conclusions and recommendations for research and development, developed in discussion groups at the symposium.

I. INTRODUCTION

There is generally a negative connotation with the use of electricity on biological systems. Electric effects on biological cells are often related to electric shocks, electric burns, or to electrocution. There is fear that exposure to electromagnetic fields may cause cancer, the opinion that electromagnetic radiation is kind of a pollutant. Much of the research on biological/medical effects of electricity has therefore concentrated on potential hazards of electromagnetic radiation, on a better understanding of damage mechanisms and remedies against them. The positive effects in bioelectrics have received much less attention, although there are spectacular research results. In the medical field, electric fields have been shown to accelerate wound healing, they are used for transdermal drug delivery, in gene therapy, and even in treatment of cancer. There are indirect effects of electric field/cell interactions, which have a positive effect on our well being. Pulsed electric fields have been shown to be useful in bacterial decontamination, an effect used for example to make our food and drinking water safer. Electric field techniques promise to be useful in bacterial decontamination of air, an important research area considering the threat of biological warfare.

In all these positive effects of electric field-cell interaction are nonthermal, that means that heating of cell suspensions or tissues can be neglected. The reason is that for many of these applications the electric fields are either very small, or the duration for which the electric field is applied is too short to cause heating. The latter is the case in the applications listed above. The spectacular results in these nonthermal techniques have been achieved with a technology which is based to a large extend on pulse power technology of the sixties and seventies. More recent advances in the generation of ultrashort electrical power pulses (pulse power technology), allow us now to extend the field of bioelectrics into a range where promising new effects of field-cell interaction can be expected. By reducing the pulse duration into the nanosecond or even shorter regime, the external electric fields in the cell become comparable and even exceed the internal electric fields, allowing us to affect processes in the cell interior without heating the cell.

The effect of ionized gases on biological cells, in physics terminology, "plasmas", was the second topic in the symposium. In nature they appear as lightning, in the laboratories and manufacturing plants as arcs and sparks. These "conventional plasmas" are violently destructive when applied to biological cells. Researchers have in the past years, however, developed "cold" high pressure plasmas, plasmas with gas temperatures close to room temperature. When applied to surfaces and gas volumes for seconds or minutes, they kill bacteria, and offer a chance to be used as sterilizing agents much simpler than conventional methods and without harming the environment.

In order to provide a forum for the exchange of information and ideas in these emerging research and technology fields the "First International Symposium on Nonthermal Medical/Biological Treatments Using electromagnetic Fields and Ionized Gases" has been held on April 12 - 14, in Norfolk, VA. The symposium was sponsored by the U.S. Air Force Office of Scientific Research, the National Science Foundation, the IEEE Nuclear and Plasma Sciences Society, the Biolectromagnetics Society, Old Dominion University, the College of William and Mary, and the Eastern Virginia Medical School. One hundred and thirty five scientists from 12 countries were attending. Eighteen Invited Talks were given covering a range from basic microbiology to pulse power technology. Approximately 60 contributed papers were presented in a poster session. The last day of the symposium was devoted to discussion on the status of the research field and strategies to expand it. The meeting was concluded with presentations on funding opportunities and application procedures. Presenters were P. Dunne for U.S. Army RD&E, R. Ellis for USDA, L. Goldberg for NSF, E. Postow for NIH, D. Quass for EPRI, and G. Roy for ONR. The session was chaired by R. Barker (AFOSR).

II. STATUS OF RESEARCH AND DEVELOPMENT

The interaction of electromagnetic fields with biological cells has been a topic of many studies since Galvani, at the end of the 18th century, explored the muscular contraction of frog legs under the influence of electric fields. With the expansion on the amplitude and frequency range of electromagnetic fields, which are now accessible and controllable by us, the possible dangers and opportunities have multiplied. There are several professional societies devoted to this topic, the most important one being the Bioelectromagnetics Society.

Although the topic of the symposium covers only a small part of bioelectromagnetic effects and treatments, only such that are based on nonthermal processes, there is still a large spectrum of research directions in this area. In order to introduce the audience, which consisted of engineers, physicists, biologists and clinicians, to these research areas we had invited prominent scientists to give tutorials and reviews on the important research areas in nonthermal treatments and on supporting pulse power and microwave technology. The sessions began with a historic overview and an introduction into fundamental concepts, presented by C. Polk, University of Rhode Island. Particularly emphasis was given to the definition of nonthermal processes at high electric fields, the topic of this conference. A classic, nonthermal medical application of pulsed electric field effects is the treatment of ventricular fibrillation by means of strong electrical shocks. A report on the latest research on ventricular fibrillation and defibrillation was presented by J. Leon, University of Montreal.

One of the most important nonthermal processes in bioelectrics is electroporation, the reversible or irreversible changes in the permeability of cell membranes due to the application of high electric fields. Basic principles of this effect were discussed by J. Weaver, MIT/Harvard, with applications given. The speaker concentrated particularly on the use of this effect for transdermal drug delivery. This topic was expanded by U. Zimmermann, University of Wuerzburg, Germany, who discussed the application of electroporation and electrofusion as a means to generate antibodies for the treatment of certain types of cancer. G. Hofmann, Genetronics Inc. carried this topic into an even more applied area, the therapeutic use of electroporation for transdermal delivery of large molecules, for gene therapy, electroporation mediated therapy of cancer, and electroporation generated delivery of drugs and genes through vessel walls for treatment of cardiovascular diseases. Following this presentation, W.R. Panje, Rush-Presbyterian-St. Luke's Medical Center, Chicago, reported about clinical trials using electroporation mediated therapy on head and neck cancer, and concluded that this method offers promising possibilities in the treatment of these cancers. Whereas controlled electroporation, the topic of these review talks has its place in therapeutic applications, uncontrolled electroporation was found to be the important mechanism in electric force injury, rather than thermal (burn) mechanisms. Research results on electric tissue injuries and consequences for their treatment were discussed by R. Lee, University of Chicago.

Theoretical considerations to the coupling of electric fields to cells were presented by K. Foster, University of Pennsylvania. His talk was particularly devoted to the effect of electrical pulses with high frequency content (ultrawideband pulses) on cell membranes and cell nuclei. Experimental results with short, high intensity electric field pulses on multicellular organisms and cells in vitro were presented by K. Schoenbach, Old Dominion University. Results of laboratory and field experiments with microsecond pulses for biofouling prevention were presented, and the potential of electric field interaction with cell nuclei for pulses in the submicrosecond range was discussed. Another application of high electric fields is the so-called Pulsed Electric Field (PEF) method, where high electric fields applied to liquid food serves to decontaminate the food. A report on the status of this rather mature technology, where industrial interest and support is in place, was given by P. Dunne, US Army Natick R&D Center.

Electrical field interaction with DNA, through coupling of the field to electron and ion transfer reactions, was discussed by M. Blank, Columbia University. He based most of the discussions on this effect on the stress protein inducing effect of low frequency magnetic fields. Many other low intensity, electric and magnetic field effects are not as well studied as the effect described by M. Blank, however are already widely used in therapeutic applications. Millimeter wave therapy e.g. is widely considered as therapeutic modality, particularly in the former Soviet Union. A review on the treatments based on low intensity millimeter wave irradiation was given by A. Pakhomov, Brooks AFB. Although seemingly effective, millimeter wave therapy is not well understood, and the research in field suffers from lack of reliable studies. The effect of intense pulses of microwave radiation on bacteria, spores and mammalian cells was the topic of a presentation by J. Kiel, AFRL, Brooks AFB. Pulsed microwave radiation in the 1.25 to 9.35 GHz range was found to affect the growth of bacteria in the presence of certain chemicals. Preliminary results suggest that pulsed microwave radiation could be directed toward pathological targets and organs while sparing normal tissue.

The presentations on electric (and magnetic) field effects on biological cells were complemented by two tutorial talks on the state of pulse power devices and high power microwave and millimeter-wave sources for possible applications in medical/biological research. The first topic, on pulsed electric power systems, was presented by M. Kristiansen, Texas Tech University. He concentrated on nanosecond and subnanosecond, pulse generators, where research institutes in Russia seem to have a leading role in expanding the source parameters to ever-shorter pulses and higher power. The status of high power microwave and millimeter wave sources and the role of pulse power technology in the development of high intensity generators were presented by E. Schamiloglu, University of New Mexico. Again, as in pulse power in general, most of dramatic increases in power are relatively recent. Only in the 1970s pulse power technology begin to emerge as an independent research field.

Whereas electrical interaction with biological cells has a long history, the use of nonthermal plasmas in atmospheric pressure air for medical/biological applications has been only recently recognized. An introduction into the physics of nonthermal plasmas, and the various types of atmospheric pressure plasmas and their features was given by E. Kunhardt, Stevens Institute of Technology. It was followed by a talk by T. C. Montie, University of Tennessee, on the application of a special type of atmospheric pressure plasma, a radio frequency driven glow discharge, for sterilization of surfaces and materials. Similar discharges, barrier discharges, have also been used for sterilization. The presentation on results of this discharge type was given by J. Birmingham, MesoSystems Technology, Inc.. For both types of plasmas the sterilization rate was reported as faster than by heat alone. The session was concluded by a talk of P. Netzer, National Naval Medical Center, on the need of new sterilization processes in healthcare, and the role of plasma methods in such an environment.

Contributed papers were presented in a poster session. The 76 accepted poster papers were placed into seven categories:

Basic Phenomena (15 contributions);
Pulsed Electric Fields (11 contributions);
Microwaves (5 contributions);
Ultraviolet Radiation (3 contributions);
Electron and Ion Beams (7 contributions);
Ionized Gases (16 contributions), and
Advanced Pulsed Power and Plasma Generators (19 contributions).

The largest research and development area represented in the poster session was bacterial decontamination, using pulsed electric fields, UV radiation, and nonthermal plasmas; the second largest area dealt with basic studies and medical applications of pulsed electric fields. The relatively large number of papers on pulsed field generators, mainly presented by scientists from the former Soviet Union, provided the audience with a good overview of leading edge pulse power systems.

Abstracts of invited and contributed papers have been published in Proceedings of this Symposium.

III. CONCLUSIONS AND RECOMMENDATIONS

Following the presentations, the status of research and development of nonthermal medical/biological treatments was discussed in four discussion sessions. Discussions concentrated on the following topics

1. Pulsed Electric Field Effects: Basic Research and Applications
2. Microwave and Millimeter Waves Interaction with Biological Cells
3. Medical Applications of Pulsed and cw Electric Field Technology
4. Ionized Gases for Biological Decontamination

The discussion sessions were chaired by J. Dunn (ALP, Chicago), J. Kiel (Brooks AFB), R. Lee (University of Chicago), and I. Alexeff (University of Tennessee).

A. Pulsed Electric Field Effects: Basic Research and Applications (J. Dunn)

The effect of pulsed electric fields on biological cells depends on pulse duration, pulse shape, and amplitude. Three pulse domains were identified, dependent on major applications and/or physical mechanisms:

1. "Traditional Electroporation":
   Ten's to hundred's of microsecond duration, several kV/cm electric fields
2. "Traditional" Biological Decontamination
   Less than 10 microsecond duration, greater 16 kV/cm electric fields
3. "Cell Modifications" Targets: cell substructures, molecules/bonds
   Submicrosecond (nanosecond, picosecond) duration; time domain is accessible with modern pulse power technology, however field-cell interaction mechanisms are not explored

The mechanism, which leads to cell death through electric field application, is not well understood. Although it is accepted that in the "traditional debacterialization" range poration of the outer membrane is the ultimate mechanism, the pore formation process itself is controversial. An approach which considers cells as perturbations in homogeneous fluid was presented by J. Dunn. It was hypothesized that electrical double layers at the cell surface cause localized heating of the cell membrane, and consequent membrane breakdown. Independent on the breakdown mechanism it was agreed that for "traditional biological decontamination", particularly in the electric field range of less than 30 kV/cm, at pulse duration of less than 2.5 microseconds, electrochemical effects can be neglected.

One of the more mature applications of PEF technique is bacterial decontamination of food, although there is still much room for better engineering of systems. Electrical requirements in food treatment depend on the type of the food. For low acid food, e.g., with a pH value of greater than 4.5, the conditions for the electrical pulses are more stringent, than for food of high acidity (pH < 4.5), where spores are absent. The dominant problem in food preservation using PEF is the high energy requirement, 100 – 400 J/ml. Improving this efficiency requires either to consider combination processing (thermal + PEF) or to search for electric field processes which are based on a mechanisms different from electroporation, such as subcellular processes or resonant molecular processes.

Collaboration among scientists in engineering biology and medicine is a key in successful research and development of PEF bacterial decontamination methods. This becomes obvious, when the results of pulsed electric field experiments on gram-positive and gram-negative bacteria, and on spores, are considered. In order to develop PEF systems for bacterial decontamination, engineers need to communicate more with biologists and physicians.

B. Microwave and Millimeter-Wave Effects (J. Kiel)

Methods using extremely short electromagnetic pulses and pulsed microwave are related. One of the main differences, which is purely technical, is seen in the coupling mechanism: direct coupling through electrodes inserted in tissue or suspensions, for high electric field pulses, and remote coupling, for microwave and millimeter wave interaction. Medical effects of microwaves and millimeter waves include post-operative septic wound healing, pain relief, treatment of hypertension, and promoting the recovery after heart attacks. Hypothermia for cancer treatment is another, however thermal, application of high power microwaves therapy. It reduces the risk for collateral (cardiovascular) damage compared to surgery and radiation treatment. Other biological effects of major interest are bacterial decontamination.

Strong fundamental research on medical and biological treatments exists in Russia and other FSU countries, and in China. Particularly, the FSU have developed a large spectrum of marketable sources for these applications. Custom made high power devices in the US range from 200 k$ to one million $. The high cost might be one of the reasons that research and development in the USA has more focused on large scale environmental (clean up of hazardous material) and industrial use (material processing, such as sintering of ceramics) by high power micro- and millimeter-wave sources. In medical research, however, the emphasis in the USA has concentrated more on the potential negative effects of micro and millimeter waves. An example is the ongoing discussion on the health and safety issues in wireless communication.

Recent developments in millimeter wave technology have provided researchers with new opportunities for work in this field. Proper scientific studies have the potential of uncovering significant benefits for all mankind. Therapeutic, health and safety applications appear to be feasible and within our reach. Preliminary reports from efforts in China, Russia, and several other countries have already produced encouraging results. Despite leading in the technological development of sources, the US is lagging behind many parts of the world in the understanding of the interaction of biological systems and microwaves. This lack of understanding is resulting in the potential loss of medical therapies (such as enhanced septic wound treating) as well as new potential health and safety issues for personal working with intense electromagnetic fields.

C. Medical Applications (R. Lee)

Medical applications in therapy and diagnostics were discussed with respect to the coupling modes of electric fields with biological systems.

1. ***Cellular Coupling*** is achieved by using relatively long pulses (> 1 ms). Applications include:

   Electrochemotherapy or Electroporation Therapy
   Electro-Transdermal Delivery
   Rhythm Disorders (defibrillation)

Cellular coupling (electroporation) is also related to electrical injury.

Corresponding to long pulses are low-frequency electric (and magnetic) fields. Applications of low frequency, cw fields are:

   Tissue ablation
   Electrical Injury (therapy)
   Electrical Stimulation

2. ***Molecular Coupling*** is considered to be the dominant mechanism when short pulses (10^{-6} to 10^{-9} s) are applied. Potential applications of such nonthermal methods are treatment of birth defects and cancer, through triggering of apoptosis.

Continuous wave treatments, using radiofrequency, microwave and optical radiation are thermal methods which have applications in:

   Musculoskeletal Heating
   Hypothermia: Treatment of Cancer
   Treatment of Burns

3. ***Atomic Coupling*** occurs for ultrashort pulses (e.g. in photolysis), and in the case of ionizing radiation, used in cancer therapy.

Diagnostic applications are ***cell sensing***:

Tissue damage and tumor detection by means of impedance spectroscopy,

Cancer cell and viral particulates by dielectrophoresis,

and ***molecular sensing***,

used in tumor detection and localization by means of conformal radiofrequency imaging.

D. Ionized Gases for Biological Decontamination (I. Alexeff)

The use of ionized gases has been demonstrated as being very effective for biological decontamination. A major US company has already a commercial product on sale. An in-depth analysis of promising decontamination technologies sponsored by the U.S. Army's Edgewood Chem-Bio Center concluded that plasmas have great potential, particularly in the areas of sensitive equipment and vehicle/shelter decontamination, but that significant development will be required before this potential can be realized.

As major applications for plasma decontamination three areas were identified:

a) bacterial decontamination in bacterial warfare,
b) sterilization of food, and
c) sterilization of medical instruments in hospitals.

The development of appropriate diagnostics for nonthermal, high-pressure air plasmas was considered as most important. As an example, there is still controversy on the role of atomic oxygen in the discharge with respect to decontamination. Whereas some claim that atomic oxygen in the high-pressure glow is extremely effective in biological contamination, others state that atomic oxygen disappears in microseconds, and so is of no effect whatsoever. However, everybody seemed to agree that identifying the killing mechanisms for bacteria, spores, and viruses is of very high priority. It is not yet clear what the most active killing species (ions, radicals, active molecules, or UV light) is.

The question of research funding was discussed. Research on these nonthermal plasmas is both basic and applied; also, since the interdisciplinary nature of the research requires teams of scientists, rather than single investigators, relatively large grant are needed. Due to the new and unique requirements for this area of research, there was no clear picture where to obtain funds. It was therefore recommended to set up a task force to develop funding.

IV. SUMMARY

The consensus of the participants was that the research field offered exciting possibilities to expand available technologies into new areas of research, and consequently has a strong potential for breakthrough results. The research discussed at the meeting carries the promise of commercial and medical applications. It is a research field to which the general public can easily relate. This was demonstrated by strong newspaper and television coverage. It seems also to have the support of our legislators. In the introductory address at the symposium, the Honorable O. Picket, ranking member in the House Subcommittee on military research promised his support for increased research spending. Members of the Virginia legislature voiced similar support.

The question of funding was addressed in the final session, where representatives of funding agencies talked about opportunities and procedures, but it was also brought up in any of the discussion sessions. Financial research support seems to be sporadic and limited. There is no interagency research program, something, which would be strongly benefit this interdisciplinary research. The lack of support is rather surprising considering the importance this research field is given in other countries, the spectacular results in clinical applications, and its commercial potential.

To explore the full potential of nonthermal treatments using electromagnetic fields and ionized gases, the topic of our symposium, the interaction and the cooperation of engineers and physicists on one side and biologists and clinicians on the other side is needed. The symposium seems to have served as a catalyst to stimulate discussions between scientists with various backgrounds but the same interest. It is hoped that these conversations lead to collaborations. The response from the participants was overwhelmingly positive, and the need for an ongoing conference was voiced. The program committee decided to hold the "Second International Symposium on Nonthermal Medical/Biological Treatments Using Electromagnetic Fields and Ionized Gases" again in Norfolk, VA, in spring of 2001, with S. Beebe, Eastern Virginia Medical School, as chair. A Special Issue of the IEEE Transactions on Plasma Science with over forty contributions on the topic of the symposium will appear in February 2,000.

ACKNOWLEDGEMENTS

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Special Issue

"Nonthermal Medical/Biological treatments Using Electromagnetic Fields and Ionized Gases". The purpose of this symposium is to bring together medical professionals, microbiologists, physicists, and electrical engineers, to exchange their experience in the field of the nonthermal bioelectrotechnologies. The format of the symposium is described in an enclosed draft of the announcement.

In order to introduce this new, interdisciplinary research field to a wider scientific community, particularly to the NPSS community, we would like to apply for a special issue on this topic in the IEEE Transactions of Plasma Science. The topic is in our opinion appropriate for the TPS, since it focuses on plasma and pulsed power physics and technology. We expect high quality contributions as evident from the list of invited speakers. We have invited eminent scientists, with background in biology, medicine, physics and engineering, to introduce the audience to their fields of research (review papers) and/or to present cutting edge results on special topics in electrobiotechnology.

So far we have verbal commitments for invited talks from:

- Charles Polk, University of Rhode Island, Keynote (Prof. Polk is editor of a book on biomedical effects of electromagnetic radiation, and editor of a section on this topic in the CRC Biomedical Engineering Handbook).
- James Weaver, Harvard/MIT, "Electroporation"
- Magne Kristiansen, Texas Tech University, "Pulsed Electrical Power Systems"
- Andrei Pakhomov, McKesson Bioservices, Brooks AFB, "Biological Effects of Millimeter Waves"
- Edl Schamiloglu, University of New Mexico, "Pulsed Microwave and Millimeter-Wave Sources'
- Erich Kunhardt, Stevens Institute of Technology, "Nonthermal Atmospheric Pressure Plasmas"
- Guenter Hofmann, Genetronics, San Diego, "Medical Applications of Electroporation"
- Patrick Dunne, US Army Natick RD&E Center, "Food Preservation with Pulsed Electric Fields"
- Yu Zengliang, Chinese Academy of Science, Hefei, China, "Ion Beam Application for Genetic Modification"

Other scientists who have tentatively agreed to give invited talks on their work are:

- Raphael Lee, University of Chicago
- Ulrich Zimmermann, University of Wuerzburg, Germany
- Patricia Netzer, National Naval Medical Center, Bethesda, MD
- Joseph Birmingham, Mesosystems, Richland, WA

We have also send out a call for contributed papers, which we plan to place in a poster session. We are confident that we will also in this category obtain contributions of high scientific quality.

Assuming that all the invited speakers will submit a manuscript, and that we will receive about the same number in contributed papers, we expect not less than 30 papers. We plan to have two reviewers for each manuscript, one from the plasma and pulse power community, one with biology and/or medical background. For the latter we count on the support of the Bioelectromagnetics Society, which has already agreed to co-sponsor our symposium.

Enclosure

Special Issue of the IEEE Transactions on Plasma Science

"Nonthermal Medical/Biological Treatments Using Electromagnetic Fields and Ionized Gases"

(Scheduled for February 2000)

Recent advances in the generation of ultrashort high power electrical pulses have opened new venues in the field of bioelectrics. Electrical pulses of duration less than a billionth of a second but at voltages exceeding ten thousand volts allow one to explore and to utilize electrical interactions with biological cells without significant heating of the tissue. The high frequency components in the ultrashort pulses have been shown to provide an effective pathway to the interior of the cells. Pulsed, high power microwave and millimeter wave sources allow one to similarly explore and utilize nonlinear processes on the *molecular* level, with the potential to some day selectively modify individual molecular structures, such as DNA.

Equally exciting is the growing field of research into the application of plasmas for chemical and biological sterilization and decontamination. A number of industrial and university research groups have already demonstrated the remarkable ability of relatively cold ionized gases to rapidly kill bacteria cells while avoiding the excessive heat and/or harsh chemicals associated with current conventional sterilization techniques. This new approach poses major advantages for both defense and commercial medical applications.

On April 12-14 1999, an international symposium will be held in Norfolk, VA, to carefully consider the tremendous opportunities growing in these new areas. In particular, a special effort will be made to use this forum to introduce M.D.s and biologists to these non-chemical treatments. Detailed information about the symposium may be found on the website www.ece.odu.edu/~emed99

The intent of the *TPS* Special Issue is to provide a wider forum for this topic and to assemble papers addressing both the fundamental and applied aspects of nonthermal electromagnetic and plasma effects on biological cells. Contributions are solicited in, but not restricted to, the following areas:

- *Electroporation of Cells and Tissues*
- *Medical Applications of Electroporation*
- *Pulsed Electric Fields for Debacterialization*
- *Interaction of High Frequency Electromagnetic Fields with Biological Systems*
- *Pulsed Microwave Induced Bioeffects*
- *Biological Effects of Millimeter Waves*
- *Air Plasma Sterilization of Surfaces and Materials*
- *Bacterial Decontamination Using High Pressure Nonthermal Discharges*

Please submit three copies of the manuscript, original figures, and a signed IEEE copyright form to one of the three guest editors whose addresses appear below. The deadline for submitting manuscripts is **May 1, 1999**. To ensure maximum speed in correspondence, please include telephone and FAX numbers and email address of the corresponding author. Further detailed instructions for authors may be found on the inside back cover of the *IEEE Transactions on Plasma Science,* and on the web: *www.IEEE.org/pubs/authors.html.*

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Guest Editorial

Special Issue on Nonthermal Medical/Biological Treatments using Electromagnetic Fields and Ionized Gases

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The interaction of electromagnetic fields with biological cells often has a negative connotation. We think of effects such as electric shocks and electric burns. There is the fear that exposure to electromagnetic fields may cause cancer, and the opinion that electromagnetic radiation is a kind of pollutant. Much of the research on biological/ medical effects of electromagnetic fields has therefore concentrated on potential **hazards** of electromagnetic radiation, on a better understanding of damage mechanisms and how to protect against them.

However, more recently the **beneficial** effects of electromagnetic interaction with biological cells are receiving more attention, particularly nonthermal effects. For example, for a long time now electric pulses have been used to save lives in cases of heart failure, but now we are finding that they can also be used to diagnose and even help to treat cancer. There are clearly effects of electric field/cell interactions, which have a positive effect on our well being. Pulsed electric fields have also been shown to be useful in bacterial decontamination, an effect used, for example, to make our food and our drinking water safer. Furthermore, they have the potential to protect us against the threats of bacterial contamination in biological warfare.

Pulsed power is the enabling technology in many of these new applications. Cancer treatment using electroporation, which is already in clinical trials, is based on the application of high power electrical pulses to malignant tumors. Bacterial decontamination of liquid food and drinking water with pulsed electric fields successfully utilizes microsecond and submicrosecond high power pulses. Research in both medical and biological applications is moving towards the use of shorter and more intense pulses where interaction with cell substructures becomes likely, and consequently exciting new effects are expected.

Resonant effects of low power microwave and millimeter waves on micro- and macro-organisms are topics of intense study, mainly in Europe. High power microwave and millimeter waves allow one to similarly explore and utilize nonlinear processes on the molecular level, with the potential to some day selectively modify molecular structures in cells. In the short wavelength range of the electromagnetic spectrum, the ultraviolet and the X-ray range, research on the effect on cells has already led to applications of pulsed power UV and X-ray sources for bacterial decontamination.

Equally exciting is the growing field of research into the application of plasmas for chemical and biological sterilization and decontamination. A number of industrial and university research groups have already demonstrated the remarkable ability of relatively cold ionized gases to rapidly kill bacteria cells while avoiding the excessive heat and/or harsh chemicals associated with current conventional sterilization techniques. This new approach poses major advantages for both defense and commercial medical applications.

In order to provide a forum for the exchange of information and ideas in these emerging research and technology fields, the "First International Symposium on Nonthermal Medical/Biological Treatments Using Electromagnetic Fields and Ionized Gases" ("ElectroMed99," for short) was held on April 12–14, 1999 in Norfolk, Virginia. The Symposium was sponsored by the U.S. Air Force Office of Scientific Research, the National Science Foundation, IEEE Nuclear and Plasma Sciences Society, the Bioelectromagnetics Society, Old Dominion University, the Eastern Virginia Medical School, and the College of William and Mary. One hundred and thirty-five scientists from twelve countries attended.

In order to introduce the audience (which consisted of engineers, physicists, biologists and clinicians) to these research areas, we had invited prominent scientists to give tutorials and reviews on the important research areas in nonthermal treatments and on the supporting plasma, pulsed power, and microwave technology. Eighteen invited talks were given in the first two days of the meeting, covering a range of topics from basic microbiology to pulsed power technology. Approximately sixty contributed papers were presented in a poster session. The largest research and development area represented in the poster session was bacterial decontamination using pulsed electric fields, UV radiation, and nonthermal plasmas. The second largest area dealt with basic studies and medical applications of pulsed electric fields. The relatively large number of papers on pulsed field generators, mainly presented by scientists from the former Soviet Union, provided the audience with a good overview of leading edge pulsed power systems.

We have placed the papers in this special issue in generally the same sequence in which they were presented at the symposium. Contributed papers are placed in topic groups following the respective lead papers. In some cases, however, we have deviated from the symposium sequence. It such cases we had the feeling that a particular sequence might make it easier for the reader to grasp a new research field.

The reader is introduced to the field of bioelectrics, the interaction of pulsed, high electric fields with cells, through five invited papers by C. Polk (U. Rhode Island), K. Foster (U. Pennsylvania), J. Weaver, (MIT/Harvard), U. Zimmermann *et al.*, (U. Wuerzburg, Germany) and S. Dev *et al.* (Genetronics, Inc.), respectively. They cover the range from fundamental effects to medical applications. Effects on cells can also be achieved with low intensity electric field as discussed in the first contributed paper by C. Liu *et al.* (U. Chengdu, China). The enabling technology for bioelectrics, pulse power technology, is introduced in an invited paper by M. Kristiansen and J. Mankowski from Texas Tech University. This paper is followed by an overview of the bioelectrics research at the Efremov Institute in St. Petersburg, Russia, by V.A. Burtsev *et al.*.

An attractive application of bioelectrics is the treatment of drinking water and liquid food with pulsed electric fields (PEF). PEF research activities in the Netherlands (van Heesch *et al.*, U. Eindhoven), the United Kingdom (S.J. McGregor *et al.*, U. Strathclyde), and Japan (S. Katsuki *et al.*, Kumamoto U.) are discussed in three following papers. Related to these methods is biofouling prevention using pulsed electric fields, a topic discussed by A. Ghazala and K.H. Schoenbach (Old Dominion U.). Pulsed electric discharges as a means to decontaminate water is discussed in a paper by Efremov et al (Triniti, Troitsk, Russia). Experimental observation on biological effects of high power microwaves are presented in an invited paper by J. Kiel *et al.* (Brooks AFB). This is complemented by a review of low intensity micro and millimeter wave effects by A. Pakhomov (McKesson BioServices) and M Murphy (Brooks AFB). Biological effects of electromagnetic fields on the molecular level are discussed in an invited paper by M. Blank and R. Goodman (Columbia U.)

The ElectroMed99 Symposium focussed on biological effects of <u>nonionizing</u> radiation. However, there is strong interest in the scientific community and in the public on the effects and applications of ionizing radiation. This field is represented in four papers, an invited paper on structural changes in cell membranes due to ionizing radiation by J. Hannig and R.C. Lee (U. Chicago), and three contributed papers on bacterial decontamination by means of pulsed light and X-rays. The papers are authored by J. Anderson *et al.* (U. Strathclyde, UK), and by McDonald *et al.*, and R. Curry *et al.*, respectively (U. Missouri).

Thirteen papers in the Special Issue are devoted to medical/biological applications of nonthermal plasmas. The Invited Papers presented at ElectroMed99 by Kunhardt, Montie, and Birmingham remain in their symposium sequence, although four new papers are inserted before Birmingham's. Readers will find Kunhardt's work to constitute a detailed review paper on the physics of air plasma generation. His discussions on the various techniques are important to anyone who would seek to apply air plasmas to medical/biological purposes. Montie's paper then provides a detailed description of just such an application; namely the use of an atmospheric pressure air plasma for the destruction of biological pathogens. The next two papers, those of M. Laroussi *et al.* and N.M. Efremov *et al.*, then describe the results they achieved with similar atmospheric pressure approaches. The paper by Kondrashova *et al.* is a bit of a "change of pace." It is inserted at this point to remind the reader of the long history of low-level air ionizers used for therapeutic (and sometimes pseudotherapeutic) purposes. Importantly, the Kondrashova team specifically demonstrates how professional medical/biological studies can move such "faddish" applications into the realm of legitimate medical therapy for the improvement of air in modern closed working environments. The paper by Kelly-Wintenberg *et al.* then maintains the theme of air quality improvement in its discussion of the novel "Volfilter" concept. This forms a convenient transition into the commercial world considerations, that Birmingham's and Hammerstrom's paper elaborates on in its presentation of various industrially oriented air plasma applications. In this similar commercial vein, the paper by L.C. Farrar *et al.* discusses large-surface air plasma decontamination/sterilization techniques. The papers by J.R. Roth *et al.* and T. Namihira *et al.* then go on to describe interesting plasma chemistry-related concepts that rely on the longevity of some of the plasma-generated active species in order to impose spatial distance between the plasma source and the desired treatment objective. In the paper by Yu.A. Kotov *et al.* results are presented that indicate how air plasma chemistry can dramatically enhance the effectiveness and utility of existing approaches using e-beams for sterilization. Finally, the Zengliang and Dubinov *et al.* papers discuss the possible mechanisms for the observed positive effects of ion bombardment of agricultural seeds.

Conclusions

The ElectroMed99 Symposium and this special issue are intended to help bridge the gap between disciplines which in the past were not considered compatible: pulsed power and microwave physics and engineering, and plasma physics on one side and biology and medicine on the other. As in any new encounter between research areas which seem fundamentally different, the language barrier between the disciplines needs to be overcome first, in order to initiate communication. Biologists and clinicians need to learn about the basics of pulsed power, electromagnetic fields, and plasma physics, in order to recognize the potential of these technologies for their research. Our colleagues in the pulsed power, microwave, and plasma science areas, on the other hand, will be confronted with unfamiliar biological and clinical terms in some of the papers that follow.

. We refer readers of this special issue to publications that emphasize biological and clinical research through the bibliographies of a series of introductory review papers. We have also asked the authors of these papers, to express and explain their methods and findings in terms, which are understandable to all the readers. We understand, however, that this is not always possible. There is the danger that through oversimplification papers lose some of their scientific value. Therefore, reading and understanding these papers requires more effort than most of our other special issues in the *IEEE Transactions on Plasma Science*. However, we hope that the reader feels that it is worth the effort. The contributions on biological and clinical issues open, in our opinion, a fascinating new research area for engineers and physicists, an area where they can make a strong impact. The "Second International Symposium on Nonthermal Medical/Biological Treatments using Electromagnetic Fields and Ionized Gases," to be held in Norfolk, VA, in spring of 2001 will again serve as forum for discussions and exchange of information on new developments in this research field.

It is our sincere hope that this Special Issue (and the ElectroMed99 symposium that spawned it) can succeed in imparting to our colleagues in the physics and electrical engineering communities some measure of the true professional and personal enthusiasm that we now hold for this exciting field of "Electromedicine." Research in this area impacts the life and health of human beings. There is no more fundamental concern. We sincerely believe that the future opportunities in this field whose dim outlines can already be perceived, are nothing short of staggering. The potential for the treatment of cancer without surgery, chemotherapy, or X-rays is, by itself, earth-shaking. When one also factors in the opportunities for rapid nonthermal sterilization/decontamination as well as possible intracellular repair it is easy to become perhaps overawed.

Therein also lies a danger - "electromedicine" has been and remains a fertile field for medical charlatans. We have all heard of cases of individuals and groups who, through either technical naivete' or greed or both, have sought to exploit the hunger for hope that fills the terminally ill and suffering. Nevertheless, the therapeutic effects of electromedicine ARE real; they simply require the serious studies and dynamic collaboration of electrical engineering/physics and medical/biological professionals in order to conclusively determine the true scope of those positive effects. The papers that appear in this issue reveal the early fruits of some pioneering collaborations. MUCH remains to be done. Many people are awaiting the answers.

Acknowledgements

First of all, we want to thank the *TPS* Editor-in-Chief, Steve Gitomer, for his agreement to host this Special Issue. We also thank Ms Hero Kotarides of Old Dominion University for her flawless administrative coordination of the manuscript collation process. We would like to thank all the reviewers. Their evaluation of the scientific merit of the manuscripts, and their helpful advice to the authors are appreciated. We, the editors, are particularly thankful for their willingness to respond quickly to our requests on sometimes multiple reviews of manuscripts. Without this responsiveness this special issue would not have been published just one year after the first announcement. Special thanks are extended to Lieutenant Colonel (LTC) (USAFR) Ralph Hill, Jr., Ph.D., of Southwest Research Institute (San Antonio, TX) for applying his unique combined expertise in both physics and biology for the incisive review of THIRTEEN of the manuscripts submitted. Finally, we as well as several of the authors of manuscripts from the former Soviet Union are particularly indebted to LTC Anne Fay (USAFR) for her careful and skillful editing of the English style and grammatical content of those papers.

Karl H. Schoenbach received the Diploma degree in physics and the Dr.rer.nat. degree in physics in 1966 and 1970, respectively, from the Technische Hochschule Darmstadt (THD), Germany. From 1970 to 1978, he was working at the THD in the areas of high-pressure gas discharge physics and on the dense plasma focus. From 1979 to 1985, he held a faculty position at Texas Tech University, where he was involved in research on fast opening switches, especially electron-beam and laser controlled diffuse discharge opening switches. In 1985, he joined Old Dominion University in Norfolk, VA. He was active in research on photoconductive switches until 1993, and has now concentrated his research efforts on high-pressure glow discharges, and on environmental and medical applications of pulsed power technology. He has organized a number of workshops and conferences, most notably the 1991 IEEE International Conference on Plasma Science. He was elected Fellow of IEEE in 1994 for "contributions to the research and development of very-high-power electronic devices".

Robert J. Barker (M'89, SM'95, Fellow'97) received the B.S. in Physics from the Stevens Institute of Technology, Hoboken, NJ, in 1971 and the M.S. and Ph.D.(under O. Buneman) in Applied Physics from Stanford University, in 1972 and 1978, respectively.

From 1978 through 1982, he worked as an on-site computational plasma physicist with G. Cooperstein's Light Ion Fusion group at the Naval Research Laboratory, Washington, DC. During that period, his collaborations with S. Goldstein resulted in several important discoveries on the fundamental nature of charged particle flow in axial and radial relativistic electron-beam pulsed power diodes. He then joined Mission Research Corporation, working with B. Goplen on improvements to both the 2D MAGIC and 3D SOS plasma simulation codes. He successfully applied those codes to explore novel accelerator and microwave source concepts.

In 1984, he began his current career as Program Manager for Plasma Physics at AFOSR. In this capacity, he actively fosters and participates in research in the areas of pulsed power, electromagnetic/electrothermal launchers, microwave/millimeter-wave generation, air plasmas, charged particle beam generation & propagation, explosive power generation, computational physics, and wargaming.

He was elected Fellow in the IEEE in 1997 and Fellow of the Air Force Research Laboratory in 1998. He is currently coediting (with E. Schamiloglu) an IEEE Press book reviewing the state-of-the-art in High Power Microwave Sources. He is a member of the American Physical Society and also a Colonel in the US Air Force Reserves, assigned to the Directed Energy Directorate of the Air Force Research Laboratory in Albuquerque, NM.

Liu Shenggang graduated from Southeast University (formerly Nanjing Polytechnic Institute) in 1955, and received the Ph.D. degree in physical electronics from the University of Electronic Science and Technology of China (UESTC, Chengdu) in 1958. He was appointed as Lecturer, Associate Professor, and Professor in 1961, 1964, and 1977, respectively. In 1980 he was elected Academician of the Chinese Academy of

Science. He was appointed as Vice-President of UESTC in 1984 and is President since 1986.

Professor Liu is Chairman of the Vacuum Electronics Society of China, Vice President of the Chinese Institute of Electronics, Chairman of the Academic Committee of the Chinese National Key Laboratory on High Power Microwaves (Beijing), Chairman of the Academic Committee of the Chinese National Key Laboratory on Intense Radiation (Chengdu), and Chairman of the Academic Committee of the Key Laboratory of the Research Institute of Electronics, Chinese Academy of Sciences (Beijing). He is a member of the International Electromagnetic Academy, MIT. He was a Distinguished Visiting Professor of the University of Tennessee, Knoxville, in 1991 and 1992, the Philips Chair Professor of the Technical University of Hamburg, Germany, a visiting professor at Leeds Polytechnic University, UK, and a visiting professor of Pohang University of Science and Technology, Korea. He is also Honorary Professor of many Chinese universities. Prof. Liu is a Fellow of IEEE since 1998.

Prof. Liu has lead various research projects on gyrotrons, free electron lasers, and plasma electronics since 1964. More recently, he has been the principal investigator of the National Key Research Project on "Basic research of microwave plasmas and their applications" funded by National Science Foundation of China. Prof. Liu is presently a Distinguished Visiting Professor at Old Dominion University and the College of William and Mary, working in the field of microhollow cathode discharges, microwave plasma excited excimer lasers, and electromagnetic field effects on biological cells.

Special Issue Papers

1. **MS-PP-18**
   Biological Applications of Large Electric Fields: Some History and Fundamentals (*Invited Paper*)
   Charles Polk

2. **MS-PP-17**
   Thermal and Nonthermal Mechanisms of Interaction of Radiofrequency Energy with Biological Systems (*Invited Paper)*
   K. Foster

3. **MS-PP-13**
   Electroporation of Cells and Tissues *(Invited Paper)*
   J. Weaver

4. **MS-PP-16**
   Electromanipulation of Mammalian Cells: Fundamentals and Applications *(Invited Paper)*
   U. Zimmermann, U. Friedrich, H. Mussauer, P. Gessner, K. Hamel, and V. Sukhorukov

5. **MS-PP-08**
   Medical Applications of Electroporation (*Invited Paper)*
   S. Dev, D. Rabussay, G. Widera, and G. Hofmann

11. MS-PP-11
   Electroporation and Increase of Cytotoxicity of Anticancer Drugs due to Low Intensity Transient Pulses
   C. Liu, B. Wang, Z. Wang, and H. Zhang

6. **MS-PP-22**
   A Review of Short Pulse Generator Technology (*Invited Paper)*
   M. Kristiansen, and J. Mankowski

7. MS-PP-05
   Development of Electrophysical Installations for Medical and Technological Applications in Efremov Institute
   V.A. Burtsev, V.A. Glukhikh, G.Sh. Manukian, and B.P. Yatsenko

8. MS-PP-10

A Fast Pulsed Power Source for Treatment of Conducting Liquids

E.J.M. van Heesch, A.J.M. Pemen, P.A.H.J. Huijbrechts, P.C.T. van der Laan, K.J. Ptasinski, G.J. Zanstra, and P. de Jong

9. MS-PP-07

Inactivation of Pathogenic and Spoilage Microorganisms in Liquids Using Pulsed Electric Fields

S.J. MacGregor, O. Farish, R. Fouracre, N.J. Rowan, and J.G. Anderson

10. MS-PP-14

Inactivation of Bacillus Stearothermophilus by Pulsed Electric Fields

S. Katsuki, T. Majima, K. Nagata, I. Lisitsyn, H. Akiyama, M. Furuta, T. Hayashi, K. Takahashi, and S. Wirkner

12. MS-PP-09

Experimental Investigation of the Action of Pulsed Electric Discharges in Liquids on Biological Objects

N.M. Efremov, B.Yu. Adamiak, V.I. Blochin, S.Ja. Dadashev, K.I. Dmitriev, V.N. Semjonov, V.F. Levashov, and V.F. Jusbashev

13. MS-PP-23

Biofouling Prevention with Pulsed Electric Fields

A. Ghazala and K.H. Schoenbach

14. MS-TF-01

Pulsed Microwave Induced Bioeffects (*Invited Paper)*

J.L. Kiel, J.E. Parker, P.J. Morales, J.L. Alls, P.A. Mason, R.L. Seaman, S.P. Mathur, and E.A. Holwitt

15. MS-TF-06

Low Intensity Millimeter Waves as a Novel Therapeutic Modality (*Invited Paper)*

A. Pakhomov and M. Murphy

16. MS-TF-02

Coupling of Low Frequency Electromagnetic Fields to Activate DNA: Stimulation of the Cellular Stress Response *(Invited Paper)*

M. Blank and R. Goodman

17. **MS-PP-21**
Structural Changes in Cell Membranes after Ionizing Electromagnetic Field Exposure *(Invited Paper)*
J. Hannig and R.C. Lee

18. MS-PP-15
Inactivation of Food-Borne Enteropathogenic Bacteria and Spoilage Fungi Using Pulsed Light
J. Anderson, N. Rowan, S. MacGregor, R. Fouracre, and O. Farish

19. MS-PP-19
The Development of Photosensitized Pulsed and Continuous Ultraviolet Decontamination Techniques for Surfaces and Solutions
K. McDonald, R. Curry, T. Clevenger, B. Brazos, and K. Unklesbay

20. MS-PP-20
The Effect of High Dose Rate X-Rays on E. Coli O157:H7 in Ground Beef
R. Curry, K. Unklesbay, N. Unklesbay, T. Clevenger, B. Brazos, G. Mesyats, and A. Filatov

21. **MS-IG-12**
Generation of Large Volume, Atmospheric Pressure, Non-Equilibrium Plasmas *(Invited Paper)*
E.E. Kunhardt

22. **MS-IG-03**
An Overview of Research Using the One Atmosphere Uniform Glow Discharge (OAUGDP) for Sterilization of Surfaces and Materials *(Invited Paper)*
T.C. Montie, K. Kelly-Wintenberg, and J. Reece Roth

23. MS-IG-07
Biological Decontamination by Non-Thermal Plasmas
M. Laroussi, I. Alexeff, E. Garate, and W. Kang

24. MS-IG-11
Action of the Selfsustained Glow Discharge in Air of Atmospheric Pressure on Biological Objects
N.M. Efremov, B.Yu. Adamiak, V.I. Blochin, S.Ja. Dadashev, K.I. Dmitriev, V.N. Semjonov, V.F. Levashov, and V.F. Jusbashev

25. MS-IG-14
The Primary Physicochemical Mechanism of Beneficial Biological/Medical Effects of Negative Air Ions

M.N. Kondrashova, E.V. Grigorenko, A.N. Tikhonov, T.V. Sirota, A.V. Temnov, and V.P. Tikhonov

26. MS-IG-04
Air Filter Sterilization Using a One Atmosphere Uniform Glow Discharge Plasma (the Volfilter)

K. Kelly-Wintenberg, D.M. Sherman, P.P.Y. Tsai, R.B. Gadri, F. Karakaya, Z. Chen, J. Reece Roth, and T.C. Montie

27. MS-IG-01
Bacterial Decontamination Using Ambient Pressure Nonthermal Discharges *(Invited Paper)*

J.G. Birmingham and D.J. Hammerstrom

28. MS-IG-13
Rapid Decontamination of Large Surface Area

L.C. Farrar, J.C. Dickens, E.A. O'Hair, and J.A. Fralick

29. MS-IG-02
A Remote Exposure Reactor (RER) for Plasma Processing and Sterilization by Plasma Active Species at One Atmosphere

J. Reece Roth, D.M. Sherman, R.B. Gadri, F. Karakaya, A. Chen, T.C. Montie, K. Kelly-Wintenberg, and P.P.Y. Tsai

30. MS-IG-08
Production of Nitric Monoxide Using Pulsed Discharges for a Medical Application

T. Namihira, S. Tsukamoto, D. Wang, S. Katsuki, H. Akiyama, K. Okamoto, and R. Hackam

31. MS-IG-10
Overview of the Application of Nanosecond Electron Beams for Radiochemical Sterilization

Yu.A. Kotov, S.Yu. Sokovnin, M.E. Balezin, Y.S. Nizhechik, and L.L. Ananicheva

32. MS-IG-15

Ion Beam for Application in Genetic Modification *(Invited Paper)*

Yu Zengliang

33. MS-IG-06

Effect of Air Plasma of Glowing Discharge on Grain Crops Seed

A.E. Dubinov, E.M. Lazarenko, and V.D. Selemir

Poster Papers

BASIC PHENOMENA

F1: Dynamic Changes of $[Ca^{2+}]_I$ in Cerebellar Granule Cells Exposed to Pulsed Electric Fields

Ya Chen, Tong Sun, Yan Wang, and Jiin-Ju Chang
Dept. Cell Biophysics, Institute of Biophysics, Chinese Academy of Sciences, Beijing, China

F2: Macroscopic Quantum Effects in Aqueous Solutions Under Low Intensity Coherent Irradiation

S. Chuksin, A. Korolev, A. Kozar, A. Sukhorukov, and M. Shtaryev
Lomonosov Moscow State University
A. Tatarintsev
Moscow Institute of Radioelectronics
S. Zenin
Medical Research Centre
I. Timochkine
Institute for High Temperatures, RAS
A. Pulino
Science Unlimited Inc., Boston, MA

F3: Definition of the Optimal Pulsed Current Intensity for the Neurological Illnesses Treatment on the Basis of Mathematical Simulation

V.T. Chemerys
Ministry of Ukraine for Science and Technology, Ukraine
V.A. Korniyenko
Medical Ambulance of Kyivo-Svyatoshin District, Kyiv Region, Ukraine

F4: The Induction of Stress Proteins for Cytoprotection in Clinical Applications

R. Goodman and M. Blank
Columbia University, New York, NY

F5: Ionizing Electromagnetic Field Poration of Cell Membranes and Surfactant Induced Sealing

J. Hannig and R. C. Lee
Department of Surgery, The University of Chicago, Chicago, IL

F6: Electroincorporation of Particles for Transdermal Delivery of Drugs

G. Hofmann and S.B. Dev
Genetronics, Inc., San Diego, CA
L. Zhang , U. Bremer, T. Spencer
Pharmetrix, Inc., Menlo Park, CA

F14: The Role of the APUD-System in the Mechanisms of the Physiological Action of Non-Heat Variable Magnetic Field

N.A. Temuryants, V.S. Martynyuk, A.V. Shekhotkin, and E.V. Evstafieva
Simferopol State University, Simferopol, Ukraine

F15: Sensitivity of Mice to Magnetic Fields Generated by Electrical Transport

N.A. Temuryants and V.S. Martynuyk
Simferopol State University, Simferopol, Ukraine
G. Villoresi
IFSI-CNR Universita "Roma Tre", Rome, Italy
N.N. Ptitsyna
FIZMIRAN, St. Peterburg, Russia

PULSED ELECTRIC FIELDS

P1: The Effect of Pulsed Electric Fields and Acoustic Shock Waves on Cells

Yu.V. Andriyanov, O.N. Andriyanova, P.V. Kozodoy, and V.P. Smirnov
Troitsk Institute of Innovation and Thermonuclear Investigation, Troitsk, Moscow Oblast, Russia
M.V. Golovanov and Ya.V. Dobrynin
Oncology Center Russian Academy of Medical Sciences, Moscow

P2: Applications of Pulsed Electric and Magnetic Fields for Prophylaxis and Treatment

Yu.V. Andriyanov
Troitsk Institute of Innovation and Thermonuclear Investigation, Troitsk, Moscow, Russia
B.A. Garilevich, Yu.V. Kudryavcev, V.I. Kirpatovsky, and A.A. Li
Central Air Force Scientific Research Hospital, Moscow

P3: Investigation of Action Produced by Pulsed Electromagnetic Fields on Biological S Systems

N.I. Boyko, L.D. Tondiy, and G.G. Kapustjanenko
R&D Group for Electromechanics and Pulsed Power, Ukraine

P4: Pulsed Electric Field (PEF) Preservation of Food Using Flexible Pulse Generator

Y.L.M. Creyghton
TNO Prins Maurits Laboratory, Rijswijk, The Netherlands
H.E. Berg
TNO Nutrition and Food Research Institute, Zeist, The Netherlands

P11: The Role of Electro-Physical Characteristics of Liquid at Pulsed Field Non-Thermal Disinfection

I. Timoshkin and U. Andres
T.H. Huxley School of Environment, Earth Science and Engineering, Imperial College of Science, Technology and Medicine, London

MICROWAVES

M1: Low-Temperature Radio-Frequency Sterilization of Medical Wastes

J.E. Bridges
Interstitial, Inc., Park Ridge, IL

M2: Diagnostic Application of Ultrashort Microwave Pulses: Confocal Microwave Imaging for Breast Cancer Detection

J.E. Bridges
Interstitial, Inc., Park Ridge, IL
S.C. Hagness
Department of Electrical and Computer Engineering, University of Wisconsin, Madison, WI
A. Taflove and M. Popovic
Dept. of Electrical and Computer Engineering, Northwestern University, Evanston, IL

M3: Electromagnetic Waves of Millimetre Range in Treatment of Diabetes

T.A. Chomazjuk, V.M. Berezovskiy, O.M. Vilyanskaya, and O.S. Chmell
National Academy of the Sciences of Ukraine

M4: Nonthermal Effect of Intense Short-Pulse Microwave Fields on Biological Objects

V.V. Ermolenko, Yu.F. Lonin, I.I. Magda, B.D. Panasenko, Yu.V. Prokopenko, S.S. Pushkaryov, and I.F. Kharchenko
NSC Kharkov Institute of Physics & Technology, Kharkov 310108, Ukraine

M5: Nonthermal Effects on Donor Blood Rytrocytes and Lymphocytes Irradiated by a H High Power Short Pulse Electromagnetic Field

Yu.F. Lonin., N.P. Dikiy, I.F. Kharchenko, V.V. Ermolenko., E.P. Medvedeva, N.I. Onishchenko, and E.A. Prasol
NSC Kharkov Institute of Physics & Technology, Kharkov, Ukraine

B2: The Use of Pulsed Electron Beams for Decontamination of Surface from Organic Compounds

I.E. Filatov and Yu.N. Novoselov

Institute of Electrophysics Ural Division of the Russian Academy of Sciences, Ekaterinburg, Russia

B3: Studies on Ion Beam Mediated Transformation of Rice and Wheat

Li, Hong, Wu. Lifang, and Yu, Zengliang

Ion Beam Bioengineering Lab, Institute of Plasma Physics, Academia Sinica, Hefei, P.R. China

B4: A Radiochemical Sterilization Using Nanosecound Electron Beams

Yu.A. Kotov and S.Yu. Sokovnin

Institute of Electrophysics, Russian Academy of Sciences, Ekaterinburg, Russia

B5: Radiochemical Sterilization of Glass Tare for Blood Products

Yu.A. Kotov, S.Yu. Sokovnin and M.E. Balezin

Institute of Electrophysics, Russian Academy of Sciences, Ekaterinburg, Russia

Y.S. Nizhechik and L.L. Ananicheva

City Blood Center SANGUIS, Ekaterinburg, Russia

B6: Studies on Ion Beam Mutation of Wheat Wide Hybridization Offspring

Wu. Lifang, Li. Hong, and Yu. Zengliang

Ion Beam Bioengineering Lab, Institute of Plasma Physics, Academia Sinica, Hefei

B7: A Concept of a Local Cancer Tissue Treatment by a Nanosecond E-Beam through a Flexible Drift Tube

V.P. Smirnov

Nuclear Fusion Institute RSC "Kurchatov Institute ", Moscow, Russia

N.A. Akhmerov, A.N. Gribov, and E.V. Grabovski

Triniti, Troitsk, Russia

E.G. Krastelev

P.N. Lebedev Physical Institute, Moscow, Russia

G7: Electrophysical Properties of Pulse Discharge with Low-Energy in the Pulse and its Action on the Biological Objects

V.L. Goruachev, A.I. Kulishevich, Ph.G. Rutberg, and V.B. Dolgo-Saburov
Institute of Problems of Electrophysics of RAS, St.Petersburg, Russia

G8: Sterilization of Medical Implements in an Ion Energy Deposition and Etching Device

J. Guillory
CSI Institute at George Mason University and Anatech Ltd.

G9: An Overview of Ozone Generation Techniques and their Applications to the M Medical Community

F. Hegeler
Department of Electrical and Computer Engineering, University of New Mexico, Albuquerque, NM

G10: Air Filter Enhancement and Sterilization Using a DC Electric Field and a One A Atmospheric Uniform Glow Discharge Plasma

D.J. Helfritch and P. Feldman
Environmental Elements Corporation, Baltimore, MD
J. Reece Roth, T.C. Montie, K. Kelly-Wintenberg, P.P.-Y. Tsai, and D.M. Shermann
The University of Tennessee, Knoxville, TN

G11: Biological & Chemical Decontamination Using an Atmospheric Pressure Plasma Jet (APPJ)

H.W. Herrmann, I. Henins, J. Park, and G.S. Selwyn
Los Alamos National Laboratory, Los Alamos, NM

G12: The Primary Physico-Chemical Mechanism of Beneficial Biological/Medical Effects of Negative Air Ions

M.N. Kondrashova, A.V. Temnov, T.V. Sirota, I.G. Stavrovskaya, I.R. Saakyan, and V.P. Tikhonov
Institute of Theoretical and Experimental Biophysics, Russian Academy Sci., Moscow Region, Russia
E.V. Grigorenko
Wake Forest University, Dept. Phys. Pharm, Winston-Salem, NC

G13: Portable Decontamination Systems Using Non-Thermal Ionized Gases

T.M. Moeller and P.M. Irving
InnovaTek, Richland, WA

A5: Development of Electrophysical Installations for Medical and Technological Applications in Efremov Institute

V.A. Burtsev, V.A. Glukhikh, and B.P. Yazenko
D.V. Efremov Scientific Research Institute of Electrophysical Apparatus, St.-Petersburg, Metallostroy, NIIEFA, Russia

A6: Pulse-Periodic Sources of Luminescent and Coherent VUV-Radiation on Dimers of Inert Gases

V.A. Burtsev, D.V. Getman, Yu. Istomin, N.I. Kazachenko, and N.V. Kalinin
D.V. Efremov Scientific Research Institute of Electrophysical Apparatus, St.-Petersburg, Metallostroy, NIIEFA, Russia

A7: Use of High di/dt Thyristors to Purify Water Using Electromagnetic Fields

J. C. Driscoll
PTS Inc., Raleigh, NC

A8: General Purpose, Fast, High Voltage Pulsers

A.K.L. Dymoke-Bradshaw, J.D. Hares and P.A. Kellett
Kentech Instruments Ltd., UK

A9: Compact Generator of Powerful Short Pulses Erina-350 for Application in Medicine and Biology

S.L. Elyash, Eh.A. Avilov, V.N. Korolev, S.P. Pukhov, and A.I. Yur'ev
Russian Federal Nuclear Center - Institute of Experimental Physics, (RFNC-VNIIEF), Sarov, Russia

A10: Small-Size Pulsed ARSA Accelerator in Medicine and Biology

S.L. Elyash, N.I .Kalinovskaya, and I.I. Karpenko
Russian Federal Nuclear Center - Institute of Experimental Physics, (RFNC-VNIIEF), Sarov, Russia

A11: Semiconductor Compact High-Voltage Sources and Accelerators for Medical/Biological Applications

E. Galstjan, L. Kazanskiy, and A. Ravaev
Moscow Radiotechnical Institute of RAS, Moscow, Russia
V. Efanov
Ioffe Physical-Technical Institute of RAS, St. Petersburg, Russia

A12: All-Solid State High Power Nano and Subnanosecond Pulse Generators on the Base of Silicon Inverse Recovery Diodes (IRD)

I.V. Grekhov, S.V. Korotkov, S.V. Shenderey, A.L. Stepaniants, and V.B. Voronkov
Ioffe Institute RAS, St.-Petersburg, Russia
B. O'Meara
Moose Hill Enterprises, Inc., Sperryville, VA

Basic Phenomena

DYNAMIC CHANGES OF $[Ca^{2+}]_i$ IN CEREBELLAR GRANULE CELLS EXPOSED TO PULSED ELECTRIC FIELDS**

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Cytosolic free calcium ion ($[Ca^{2+}]_i$) is an important second messenger for calcium signalling sensitive to a wide variety of environmental stimuli. It is interesting to study changes of $[Ca^{2+}]_i$ caused by electromagnetic field in understanding the mechanism of the interaction between external electromagnetic field and living cells. Up to now some experimental results have shown that external field with low frequency is effective in modifying $[Ca^{2+}]_i$ fluxes (Walleczek, 1992) and change of $[Ca^{2+}]_i$ depends not only on frequency but also on the field intensities (Blackman et al., 1985). Experiments have also shown the possibility that an external electromagnetic field affects cells through the intracellular signaling pathway of the G-protein. To describe the influence on $[Ca^{2+}]_i$, Eichwald and Kaiser (1995) have established a theoretical model based on the process of release of $[Ca^{2+}]_i$ induced by IP3. By using radio-immunoassay (RIA) and Fura2/AM ratio fluorescent method, we have observed that cytosolic CAMP (cyclic Adenosine Monophosphate) in suspended chicken embryonic brain cells exposed to a single electric pulse decreased and $[Ca^{2+}]_i$ level increased. Also $[Ca^{2+}]_i$ level was increased where the pulsation solution was free of Ca^{2+} (Shen et al., 1997).

The aim of this paper is to study temporal and spatial $[Ca^{2+}]_i$ changes induced by pulsed electric fields using Confocal laser scanning microscope and fluorescent microscope supplied with CCD video imaging system. Cultured chicken cerebrellar granule cells were loaded with fluo-3/AM and exposed to a single electric pulse (SEP). Two image acquisitive modes, the point-scanning mode (PSM) and the frame-scanning mode (FSM), were used to study the dynamic changes of$[Ca^{2+}]_i$ induced by SEP stimulation. The results showed that following the stimulation, $[Ca^{2+}]_i$ increased immediately when the external media containing $[Ca^{2+}]_i$ and pulsed electric field also can induce $[Ca^{2+}]_i$ rise after adding EGTA to chelate the extracellular Ca^{2+} or adding $LaCl_3$ to block calcium channels in the external media. All these results indicated that the increases of $[Ca^{2+}]_i$ were partially due to cellular endogenous calcium suggesting that the IP3 signaling pathway might be opened by external electric fields. With the increase of field intensity from 0.25KV/cm to 2.0KV/cm, the elevated rate of fluorescent intensity increased. However, the rate at 1.0KV/cm was significantly decreased. The calorimetric assay of Ca^{2+}- ATPase activities revealed that Ca^{2+}- ATPase in plasma membrane was activated significantly by SEP in this intensity.

Key words: pulsed electric field, $[Ca^{2+}]_i$, Ca^{2+}-ATPase , granule cells, embryonic chick, fluo-3/AM, Confocal laser scanning microscope;

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DEFINITION OF THE OPTIMAL PULSED CURRENT INTENSITY FOR THE NEUROLOGICAL ILLNESSES TREATMENT ON THE BASIS OF MATHEMATICAL SIMULATION

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Pulsed currents of relatively weak intensity have been used in the medical treatment of neurological illnesses. The mechanism of current action is complex and includes some thermal effects and some biochemical effects. Often the latter have not had proper evaluation, and the dose of recommended current processing is sometimes not grounded in necessity. Exceeding the permissible level of pulsed current is liable to aggravate phenomena. Example: patient N., 53 years old, was undergoing treatment by the diathermic pulsed currents for neuralgia of a shoulder, connected with some violations in the thorax area of the spinal column. During the processing by the sewn-on electrodes, a pulsed current dose was extremely excessive compared to the allowable in this case. As a result, the patient received serious damage to nervous channels displayed through occasional visible swelling of the larynx, and loss of voice. Intensive anti-inflammation and anti-allergic therapy was needed to overcome these negative consequences. This leads to the conclusion that medical personnel do not have enough understanding of the possible deep influence of the pulsed current on the organism.

To study this influence, complex electrodynamic and electrophysiological investigations are necessary. The authors find this a great opportunity for numeric simulation of pulsed current passage using mathematical models of electromagnetic fields in a non-uniform continuum, with additional correlations to account for internal processes in a medium stipulated by current. As the primary condition for a numerical methods of finite elements application, the authors needed a 3D structural model of a human body build anatomically accessible for every researcher who would like to apply the electromagnetic theory methods to it. Such a model must be constructed in the terms of finite element tools with designation of electrophysical and electrophysiological properties of every specific area of body and with possible transition to a 2D cross section if necessary.

The several well known commercial programs of unstable electromagnetic phenomena simulation are discussed from the point of view of their applicability in the study of a pulsed current passing through physiological objects. Unfortunately, although 2D program software are accessible and moderately inexpensive, the 3D program software is very costly and requires a more powerful computer for implementation. The simple examples of 2D current distributions show the different strongly unhomogeneous current flowing in the area and demonstrate the possible concentration of current density with a corresponding increase of a physiological action. The main purpose of future investigations in this field is to establish the measure of a permissible dose of pulsed current processing—based on the simulation of a current distribution and connected biological actions.

IONIZING ELECTROMAGNETIC FIELD PORATION OF CELL MEMBRANES AND SURFACTANT INDUCED SEALING

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Introduction: Radiating high-energy electromagnetic pulses (>124 eV) produce reactive oxygen intermediates (ROI) in tissues through ionization of H_2O. Associated with the water ionizition is an energy dissipation typically in the range of about 33 eV, enough to break a strong chemical bond. Thus ionizing radiation damages chemical structures in biological tissue by a direct mechanism as well as through follow-up chemical reactions of the free-radical ions.[1] Our research focuses on characterization and therapy for free-radical mediated peroxidation of the lipids and proteins of the cell membranes that cause damage in the structure and function of the membrane. In search for a clinical therapy against the lethal consequences of ionizing pulsed field exposure, we are investigating the potential of surfactants from the class of non-ionic tri-block co-polymers to seal radiation-permeabilized cell membranes.[2] Here we report results on increased dye leakage from calcein loaded irradiated skeletal muscle cells after post-radiation and surfactant treatment effects.

Materials and Methods: Primary isolated rat skeletal muscle cells were loaded with calcein and monitored on a Nikon inverted microscope equipped with fluorescent optics ($\lambda_{ex} = 490$ nm, $\lambda_{em} = 520$ nm). Fluorescent images were recorded to a PC using a CCD camera and a digitizing board. After establishing baseline fluorescence levels cells were irradiated with 160 Gy using a ^{60}Co source (1.17 and 1.33 MeV, Gammacell® 220, AECL, Chalk River, Ontario). Cell fluorescence intensity was monitored up to 120 minutes post-exposure to evaluate dye leakage secondary to membrane permeability changes. Images were analyzed by a custom image-processing program to determine dye intensity over the entire cell including corrections for background fluorescence and normalization to baseline cell fluorescence levels. To test for surfactant sealing effects Poloxamer 188 (P188, 0.1 mM) was added to the culture media at ten minutes post-radiation. P188 (M_r 8400, BASF, Parsippany, NJ) is an amphiphilic tri-block, linear polymer.[3]

Results: Cell membrane changes due to ionizing radiation become microscopically visible during the first two hours in the form of blebs appearing on the surface of the skeletal muscle cells. With an average delay time of 34 ±3 minutes the dye starts leaking out of the cell. The time resolved leakage thereafter follows a mono-exponential curve which we could quantitatively describe with a two compartment diffusion model. Using this model a time constant characteristic for the dye leakage was calculated to $\tau = 7.5 \pm 0.2$ minutes. The addition of P188 to the cell medium completely inhibited the dye loss after irradiation over the same time course. More recent results indicate that the observed P188 sealing effect can be translated into enhanced cell survival of muscle cells after ionizing pulsed field exposure.

Conclusion: These data demonstrate that ionizing pulsed fields affect the structure and function of lipid bilayer membranes resulting in increased permeability. P188 and, we presume, other similar amphiphilic molecules have properties that are effective for reducing the membrane damage due to radiating high-energy pulses and thereby prolong cell survival.

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THE EFFECT OF MAGNETIC RESONANCE ON THE REGENERATION OF THE SCIATIC NERVE OF MICE *IN VITRO*

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Nerve regeneration is possible, provided that the damage occurs outside the central nervous system (CNS) and the neutron cell body is intact and unharmed. The magnetic fields used in this study were generated by Jacobson's magnetic Resonance Device, which consists of two 18-inch diameter coils of 30 gauge copper wire connected in series (Helmholtz configuration), placed 9 inches apart. The coils were connected to a power supply and an attenuator to obtain the desired field in the space between the coils. The magnetic field strength (flux densities) were calculated from the equation mc^2 Bvlq (Jacobson's Equation). In this study 24 sciatic nerves of mice were surgically excised under aseptic conditions. The nerves were placed individually in flasks containing 15 ml of DMEM with high glucose) L-glutamine, 110 ml/L, sodium pyruvate, and pyridoxine hydrochloride. The flasks were stored in a 5% C02 incubator at 37 degrees C. Six nerves served as control and were not exposed to magnetic fields. Six of the remaining 18 nerves (El - E6) were exposed to 14 signals for 3 min per signal for a total of 42 min each day. Five nerves (E7 E11) were exposed to 20 signals for 3 minutes per signal for a total of 60 mm each day. The remaining seven nerves (E12-E18) were exposed to individual signals for 40 min each (Table I). The experimental nerves were exposed for a total of 10 days over a period of' 5 days. At the end of the 15 day period, the experimental nerves appeared wider and thicker than control nerves, under a phase contrast microscope. In addition the experimental nerves retained a dense structure and displayed more dendritic growth than the control nerves, which showed much disintegration. Three control and three experimental nerves were randomly chosen for DNA analysis. DNA was extracted as described by Amersham Pharmacia Biotech and gel electrophoresis tests were run on the extracted DNA samples. A thick band of DNA was visible in both the control and experimental nerve DNA samples which leads to the conclusion that magnetic fields do not cause DNA degradation. The remaining 18 nerves were cut into two halves, one set of which was prepared for light and electron microscopy, and the other for paraffin sectioning. The light and electron microscope sections revealed a regular distribution of myelinated axons in the experimental nerves. In contrast, the axons of the control nerves had an irregular shape, were fewer in number, and had a very narrow band of myelination. The paraffin sections were stained with MIB-l, a diagnostic marker that stains a proliferation associated nuclear antigen. Both the experimental and the control nerves stained negative for the MIB-1 marker, implying that magnetic fields do not lead to uncontrolled cell proliferation The results of this study provide evidence that magnetic fields applied at picoTesla ranges allowed the nerves to preserve their subcellular Structures without uncontrolled proliferation.

This work was supported by the Department of Applied Medical Physics and Neuromagnetics in Boca Raton, Florida.

ENHANCED ELECTROPORATION-MEDIATED DNA DELIVERY VIA CELL MEMBRANE MODIFICATION USING ENERGY-REGULATED ALPHA PARTICLE RADIATION

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Electroporation is a commonly used technique to introduce DNA and other large macromolecules into cells and is emerging as a promising mechanism for therapeutic gene-, and drug-delivery. Even though this technique sees widespread application, the fundamental mechanisms of electroporation-induced membrane permeability are still frequently debated. Based upon a few studies reported in the literature, we have investigated the possibility of improving electroporation efficiency by developing stress sites within the cellular membrane using carefully modulated impingements of ionizing radiation. Ionizing radiation, in the form of energy-regulated alpha-particles, is focused upon the proximal cellular membrane or targeted cells, while carefully minimizing further penetration of the alpha-particles into the cells where cytotoxic-, organellular-, and nuclear-damage may result. Alpha-particle energy is regulated by allowing the particles to pass through thin, energy-absorbing material layers positioned between an isotopic alpha-particle source and targeted cells. The resultant localized damage provides a stress site in the membrane that increases the effectiveness of subsequent material delivery into the cell using electroporation.

Using very low dose exposure (typically <20 alpha impingements per cell), we have demonstrated that this treatment can enhance electroporation-mediated plasmid transport, in some instances by 200%. Further, the radiation treatment of targeted membranes may enhance survivability of the cells by reducing the trauma experienced by the cells during the electroporation process. Improved material delivery coupled with potential increased survivability serves to increase the overall efficiency of electroporation-mediated cellular transformation; thus enhancing the potential of this widely used technique.

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ELECTOPORATION MEDIATED GENE DELIVERY INTO TUMOR CELLS *IN VIVO*

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Introduction: The technique of *in vivo* gene transfer has gathered a great deal of momentum recently but most of the approved procedures involve viral vectors. Non-viral gene transfer methods, which have many advantages, are being increasingly used and include direct injection of plasmid DNA. The use of cationic liposomes and also electroporation (EP) which is a standard laboratory method of introducing exogenous molecules into cells by pulsed electric fields have been shown to be highly efficient. We have reported elsewhere ([1,2]) the delivery of both marker (*lacZ*) and functional genes (MCP-1) into the C6 gliomas of rats *in situ* by *in vivo* electroporation. We report here results of *in vivo* delivery of luciferase gene (plasmid: pGL3) and a mutant Green Fluorescent Protein gene (plasmid: pEGFP-C1) into brain tumors.

Method: Subcutaneous tumors (~8mm) are grown in both flanks of Wistar rats (~160g) by inoculation of 100 μl of cell pellet (C6 glioma cell lines obtained from the ATCC). On day five, 25 μg of the plasmid in 100 μl of KPBS is directly injected into the exposed tumor and pulsed from a BTX (San Diego, CA) square wave electroporation fitted with a 0.5 cm needle array and a manual switch to rotate the electric field. The two controls for each plasmid are EP only and plasmid injection only.

Altogether, eight groups of samples have been run for the luciferase gene expression and the pulse parameters that gave the highest gene expression have been used for the mutant green fluorescent protein. In each case, tumors are excised 48 hours after the gene transfer. For the pGL3 (Promega), tissues are minced and immediately frozen in pulverized dry ice. Before measurement of gene expression, samples are thawed and 2 ml of luciferase lysis buffer is added to each sample. The each is homogenized, incubated for 30 min at room temperature and centrifuged at 15,000 rpm for 30 minutes. 100 μl of the substrate, provided in the Promega assay kit, is mixed with 20 μl of the supernatant sample and the mixture is used for measurement of luciferase activity using a luminometer. For the GFP (Clonetech), 48 hours after gene transfer, rat is perfused with PBS and 4% paraformaldehyde PBS. Tumors are cut and fixed with paraformaldehyde overnight. After washing off the PBS, tumors are sliced (100 μm) with a vibratome and GFP expression visualized with a confocal microscope with excitation at 488 nm.

Results: Of the eight different combinations of pulse parameters used for the luciferase experiments, 75V and 8 x 10 ms pulses shows the highest mean light unit reading- 132 fold greater compared to the control (injection of plasmid only and no electroporation). Results are statistically significant at the level of $p = 0.01$. The pulsed tumors with the injected GFP showed bright green light over a very wide area of the tumor tissue in contrast to only a few spots of green light in the GFP "injection only" control sample.

Conclusions: A plasmid DNA injection directly into tumors, followed by *in vivo, in situ*, electroporation can dramatically enhance gene expression, compared to the injection of plasmid only, clearly demonstrating its potential for gene therapy for solid tumors.

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Special Issue of the IEEE Transactions on Plasma Science

"Nonthermal Medical/Biological Treatments Using Electromagnetic Fields and Ionized Gases"

(Scheduled for February 2000)

Recent advances in the generation of ultrashort high power electrical pulses have opened new venues in the field of bioelectrics. Electrical pulses of duration less than a billionth of a second but at voltages exceeding ten thousand volts allow one to explore and to utilize electrical interactions with biological cells without significant heating of the tissue. The high frequency components in the ultrashort pulses have been shown to provide an effective pathway to the interior of the cells. Pulsed, high power microwave and millimeter wave sources allow one to similarly explore and utilize nonlinear processes on the *molecular* level, with the potential to some day selectively modify individual molecular structures, such as DNA.

Equally exciting is the growing field of research into the application of plasmas for chemical and biological sterilization and decontamination. A number of industrial and university research groups have already demonstrated the remarkable ability of relatively cold ionized gases to rapidly kill bacteria cells while avoiding the excessive heat and/or harsh chemicals associated with current conventional sterilization techniques. This new approach poses major advantages for both defense and commercial medical applications.

On April 12-14 1999, an international symposium will be held in Norfolk, VA, to carefully consider the tremendous opportunities growing in these new areas. In particular, a special effort will be made to use this forum to introduce M.D.s and biologists to these non-chemical treatments. Detailed information about the symposium may be found on the website www.ece.odu.edu/~emed99

The intent of the *TPS* Special Issue is to provide a wider forum for this topic and to assemble papers addressing both the fundamental and applied aspects of nonthermal electromagnetic and plasma effects on biological cells. Contributions are solicited in, but not restricted to, the following areas:

- *Electroporation of Cells and Tissues*
- *Medical Applications of Electroporation*
- *Pulsed Electric Fields for Debacterialization*
- *Interaction of High Frequency Electromagnetic Fields with Biological Systems*
- *Pulsed Microwave Induced Bioeffects*
- *Biological Effects of Millimeter Waves*
- *Air Plasma Sterilization of Surfaces and Materials*
- *Bacterial Decontamination Using High Pressure Nonthermal Discharges*

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Guest Editorial

Special Issue on Nonthermal Medical/Biological Treatments using Electromagnetic Fields and Ionized Gases

by

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The interaction of electromagnetic fields with biological cells often has a negative connotation. We think of effects such as electric shocks and electric burns. There is the fear that exposure to electromagnetic fields may cause cancer, and the opinion that electromagnetic radiation is a kind of pollutant. Much of the research on biological/ medical effects of electromagnetic fields has therefore concentrated on potential **hazards** of electromagnetic radiation, on a better understanding of damage mechanisms and how to protect against them.

However, more recently the **beneficial** effects of electromagnetic interaction with biological cells are receiving more attention, particularly nonthermal effects. For example, for a long time now electric pulses have been used to save lives in cases of heart failure, but now we are finding that they can also be used to diagnose and even help to treat cancer. There are clearly effects of electric field/cell interactions, which have a positive effect on our well being. Pulsed electric fields have also been shown to be useful in bacterial decontamination, an effect used, for example, to make our food and our drinking water safer. Furthermore, they have the potential to protect us against the threats of bacterial contamination in biological warfare.

Pulsed power is the enabling technology in many of these new applications. Cancer treatment using electroporation, which is already in clinical trials, is based on the application of high power electrical pulses to malignant tumors. Bacterial decontamination of liquid food and drinking water with pulsed electric fields successfully utilizes microsecond and submicrosecond high power pulses. Research in both medical and biological applications is moving towards the use of shorter and more intense pulses where interaction with cell substructures becomes likely, and consequently exciting new effects are expected.

Resonant effects of low power microwave and millimeter waves on micro- and macro-organisms are topics of intense study, mainly in Europe. High power microwave and millimeter waves allow one to similarly explore and utilize nonlinear processes on the molecular level, with the potential to some day selectively modify molecular structures in cells. In the short wavelength range of the electromagnetic spectrum, the ultraviolet and the X-ray range, research on the effect on cells has already led to applications of pulsed power UV and X-ray sources for bacterial decontamination.

Equally exciting is the growing field of research into the application of plasmas for chemical and biological sterilization and decontamination. A number of industrial and university research groups have already demonstrated the remarkable ability of relatively cold ionized gases to rapidly kill bacteria cells while avoiding the excessive heat and/or harsh chemicals associated with current conventional sterilization techniques. This new approach poses major advantages for both defense and commercial medical applications.

In order to provide a forum for the exchange of information and ideas in these emerging research and technology fields, the "First International Symposium on Nonthermal Medical/Biological Treatments Using Electromagnetic Fields and Ionized Gases" ("ElectroMed99," for short) was held on April 12–14, 1999 in Norfolk, Virginia. The Symposium was sponsored by the U.S. Air Force Office of Scientific Research, the National Science Foundation, IEEE Nuclear and Plasma Sciences Society, the Bioelectromagnetics Society, Old Dominion University, the Eastern Virginia Medical School, and the College of William and Mary. One hundred and thirty-five scientists from twelve countries attended.

In order to introduce the audience (which consisted of engineers, physicists, biologists and clinicians) to these research areas, we had invited prominent scientists to give tutorials and reviews on the important research areas in nonthermal treatments and on the supporting plasma, pulsed power, and microwave technology. Eighteen invited talks were given in the first two days of the meeting, covering a range of topics from basic microbiology to pulsed power technology. Approximately sixty contributed papers were presented in a poster session. The largest research and development area represented in the poster session was bacterial decontamination using pulsed electric fields, UV radiation, and nonthermal plasmas. The second largest area dealt with basic studies and medical applications of pulsed electric fields. The relatively large number of papers on pulsed field generators, mainly presented by scientists from the former Soviet Union, provided the audience with a good overview of leading edge pulsed power systems.

We have placed the papers in this special issue in generally the same sequence in which they were presented at the symposium. Contributed papers are placed in topic groups following the respective lead papers. In some cases, however, we have deviated from the symposium sequence. It such cases we had the feeling that a particular sequence might make it easier for the reader to grasp a new research field.

The reader is introduced to the field of bioelectrics, the interaction of pulsed, high electric fields with cells, through five invited papers by C. Polk (U. Rhode Island), K. Foster (U. Pennsylvania), J. Weaver, (MIT/Harvard), U. Zimmermann *et al.*, (U. Wuerzburg, Germany) and S. Dev *et al.* (Genetronics, Inc.), respectively. They cover the range from fundamental effects to medical applications. Effects on cells can also be achieved with low intensity electric field as discussed in the first contributed paper by C. Liu *et al.* (U. Chengdu, China). The enabling technology for bioelectrics, pulse power technology, is introduced in an invited paper by M. Kristiansen and J. Mankowski from Texas Tech University. This paper is followed by an overview of the bioelectrics research at the Efremov Institute in St. Petersburg, Russia, by V.A. Burtsev *et al.*.

An attractive application of bioelectrics is the treatment of drinking water and liquid food with pulsed electric fields (PEF). PEF research activities in the Netherlands (van Heesch *et al.*, U. Eindhoven), the United Kingdom (S.J. McGregor *et al.*, U. Strathclyde), and Japan (S. Katsuki *et al.*, Kumamoto U.) are discussed in three following papers. Related to these methods is biofouling prevention using pulsed electric fields, a topic discussed by A. Ghazala and K.H. Schoenbach (Old Dominion U.). Pulsed electric discharges as a means to decontaminate water is discussed in a paper by Efremov et al (Triniti, Troitsk, Russia). Experimental observation on biological effects of high power microwaves are presented in an invited paper by J. Kiel *et al.* (Brooks AFB). This is complemented by a review of low intensity micro and millimeter wave effects by A.. Pakhomov (McKesson BioServices) and M Murphy (Brooks AFB). Biological effects of electromagnetic fields on the molecular level are discussed in an invited paper by M. Blank and R. Goodman (Columbia U.)

The ElectroMed99 Symposium focussed on biological effects of <u>nonionizing</u> radiation. However, there is strong interest in the scientific community and in the public on the effects and applications of ionizing radiation. This field is represented in four papers, an invited paper on structural changes in cell membranes due to ionizing radiation by J. Hannig and R.C. Lee (U. Chicago), and three contributed papers on bacterial decontamination by means of pulsed light and X-rays. The papers are authored by J. Anderson *et al.* (U. Strathclyde, UK), and by McDonald *et al.*, and R. Curry *et al.*, respectively (U. Missouri).

Thirteen papers in the Special Issue are devoted to medical/biological applications of nonthermal plasmas. The Invited Papers presented at ElectroMed99 by Kunhardt, Montie, and Birmingham remain in their symposium sequence, although four new papers are inserted before Birmingham's. Readers will find Kunhardt's work to constitute a detailed review paper on the physics of air plasma generation. His discussions on the various techniques are important to anyone who would seek to apply air plasmas to medical/biological purposes. Montie's paper then provides a detailed description of just such an application; namely the use of an atmospheric pressure air plasma for the destruction of biological pathogens. The next two papers, those of M. Laroussi *et al.* and N.M. Efremov *et al.*, then describe the results they achieved with similar atmospheric pressure approaches. The paper by Kondrashova *et al.* is a bit of a "change of pace." It is inserted at this point to remind the reader of the long history of low-level air ionizers used for therapeutic (and sometimes pseudotherapeutic) purposes. Importantly, the Kondrashova team specifically demonstrates how professional medical/biological studies can move such "faddish" applications into the realm of legitimate medical therapy for the improvement of air in modern closed working environments. The paper by Kelly-Wintenberg *et al.* then maintains the theme of air quality improvement in its discussion of the novel "Volfilter" concept. This forms a convenient transition into the commercial world considerations, that Birmingham's and Hammerstrom's paper elaborates on in its presentation of various industrially oriented air plasma applications. In this similar commercial vein, the paper by L.C. Farrar *et al.* discusses large-surface air plasma decontamination/sterilization techniques. The papers by J.R. Roth *et al.* and T. Namihira *et al.* then go on to describe interesting plasma chemistry-related concepts that rely on the longevity of some of the plasma-generated active species in order to impose spatial distance between the plasma source and the desired treatment objective. In the paper by Yu.A. Kotov *et al.* results are presented that indicate how air plasma chemistry can dramatically enhance the effectiveness and utility of existing approaches using e-beams for sterilization. Finally, the Zengliang and Dubinov *et al.* papers discuss the possible mechanisms for the observed positive effects of ion bombardment of agricultural seeds.

Conclusions

The ElectroMed99 Symposium and this special issue are intended to help bridge the gap between disciplines which in the past were not considered compatible: pulsed power and microwave physics and engineering, and plasma physics on one side and biology and medicine on the other. As in any new encounter between research areas which seem fundamentally different, the language barrier between the disciplines needs to be overcome first, in order to initiate communication. Biologists and clinicians need to learn about the basics of pulsed power, electromagnetic fields, and plasma physics, in order to recognize the potential of these technologies for their research. Our colleagues in the pulsed power, microwave, and plasma science areas, on the other hand, will be confronted with unfamiliar biological and clinical terms in some of the papers that follow.

. We refer readers of this special issue to publications that emphasize biological and clinical research through the bibliographies of a series of introductory review papers. We have also asked the authors of these papers, to express and explain their methods and findings in terms, which are understandable to all the readers. We understand, however, that this is not always possible. There is the danger that through oversimplification papers lose some of their scientific value. Therefore, reading and understanding these papers requires more effort than most of our other special issues in the *IEEE Transactions on Plasma Science*. However, we hope that the reader feels that it is worth the effort. The contributions on biological and clinical issues open, in our opinion, a fascinating new research area for engineers and physicists, an area where they can make a strong impact. The "Second International Symposium on Nonthermal Medical/Biological Treatments using Electromagnetic Fields and Ionized Gases," to be held in Norfolk, VA, in spring of 2001 will again serve as forum for discussions and exchange of information on new developments in this research field.

It is our sincere hope that this Special Issue (and the ElectroMed99 symposium that spawned it) can succeed in imparting to our colleagues in the physics and electrical engineering communities some measure of the true professional and personal enthusiasm that we now hold for this exciting field of "Electromedicine." Research in this area impacts the life and health of human beings. There is no more fundamental concern. We sincerely believe that the future opportunities in this field whose dim outlines can already be perceived, are nothing short of staggering. The potential for the treatment of cancer without surgery, chemotherapy, or X-rays is, by itself, earth-shaking. When one also factors in the opportunities for rapid nonthermal sterilization/decontamination as well as possible intracellular repair it is easy to become perhaps overawed.

Therein also lies a danger - "electromedicine" has been and remains a fertile field for medical charlatans. We have all heard of cases of individuals and groups who, through either technical naivete' or greed or both, have sought to exploit the hunger for hope that fills the terminally ill and suffering. Nevertheless, the therapeutic effects of electromedicine ARE real; they simply require the serious studies and dynamic collaboration of electrical engineering/physics and medical/biological professionals in order to conclusively determine the true scope of those positive effects. The papers that appear in this issue reveal the early fruits of some pioneering collaborations. MUCH remains to be done. Many people are awaiting the answers.

Acknowledgements

First of all, we want to thank the *TPS* Editor-in-Chief, Steve Gitomer, for his agreement to host this Special Issue. We also thank Ms Hero Kotarides of Old Dominion University for her flawless administrative coordination of the manuscript collation process. We would like to thank all the reviewers. Their evaluation of the scientific merit of the manuscripts, and their helpful advice to the authors are appreciated. We, the editors, are particularly thankful for their willingness to respond quickly to our requests on sometimes multiple reviews of manuscripts. Without this responsiveness this special issue would not have been published just one year after the first announcement. Special thanks are extended to Lieutenant Colonel (LTC) (USAFR) Ralph Hill, Jr., Ph.D., of Southwest Research Institute (San Antonio, TX) for applying his unique combined expertise in both physics and biology for the incisive review of THIRTEEN of the manuscripts submitted. Finally, we as well as several of the authors of manuscripts from the former Soviet Union are particularly indebted to LTC Anne Fay (USAFR) for her careful and skillful editing of the English style and grammatical content of those papers.

Karl H. Schoenbach received the Diploma degree in physics and the Dr.rer.nat. degree in physics in 1966 and 1970, respectively, from the Technische Hochschule Darmstadt (THD), Germany. From 1970 to 1978, he was working at the THD in the areas of high-pressure gas discharge physics and on the dense plasma focus. From 1979 to 1985, he held a faculty position at Texas Tech University, where he was involved in research on fast opening switches, especially electron-beam and laser controlled diffuse discharge opening switches. In 1985, he joined Old Dominion University in Norfolk, VA. He was active in research on photoconductive switches until 1993, and has now concentrated his research efforts on high-pressure glow discharges, and on environmental and medical applications of pulsed power technology. He has organized a number of workshops and conferences, most notably the 1991 IEEE International Conference on Plasma Science. He was elected Fellow of IEEE in 1994 for "contributions to the research and development of very-high-power electronic devices".

Robert J. Barker (M'89, SM'95, Fellow'97) received the B.S. in Physics from the Stevens Institute of Technology, Hoboken, NJ, in 1971 and the M.S. and Ph.D.(under O. Buneman) in Applied Physics from Stanford University, in 1972 and 1978, respectively.

From 1978 through 1982, he worked as an on-site computational plasma physicist with G. Cooperstein's Light Ion Fusion group at the Naval Research Laboratory, Washington, DC. During that period, his collaborations with S. Goldstein resulted in several important discoveries on the fundamental nature of charged particle flow in axial and radial relativistic electron-beam pulsed power diodes. He then joined Mission Research Corporation, working with B. Goplen on improvements to both the 2D MAGIC and 3D SOS plasma simulation codes. He successfully applied those codes to explore novel accelerator and microwave source concepts.

In 1984, he began his current career as Program Manager for Plasma Physics at AFOSR. In this capacity, he actively fosters and participates in research in the areas of pulsed power, electromagnetic/electrothermal launchers, microwave/millimeter-wave generation, air plasmas, charged particle beam generation & propagation, explosive power generation, computational physics, and wargaming.

He was elected Fellow in the IEEE in 1997 and Fellow of the Air Force Research Laboratory in 1998. He is currently coediting (with E. Schamiloglu) an IEEE Press book reviewing the state-of-the-art in High Power Microwave Sources. He is a member of the American Physical Society and also a Colonel in the US Air Force Reserves, assigned to the Directed Energy Directorate of the Air Force Research Laboratory in Albuquerque, NM.

Liu Shenggang graduated from Southeast University (formerly Nanjing Polytechnic Institute) in 1955, and received the Ph.D. degree in physical electronics from the University of Electronic Science and Technology of China (UESTC, Chengdu) in 1958. He was appointed as Lecturer, Associate Professor, and Professor in 1961, 1964, and 1977, respectively. In 1980 he was elected Academician of the Chinese Academy of

Science. He was appointed as Vice-President of UESTC in 1984 and is President since 1986.

Professor Liu is Chairman of the Vacuum Electronics Society of China, Vice President of the Chinese Institute of Electronics, Chairman of the Academic Committee of the Chinese National Key Laboratory on High Power Microwaves (Beijing), Chairman of the Academic Committee of the Chinese National Key Laboratory on Intense Radiation (Chengdu), and Chairman of the Academic Committee of the Key Laboratory of the Research Institute of Electronics, Chinese Academy of Sciences (Beijing). He is a member of the International Electromagnetic Academy, MIT. He was a Distinguished Visiting Professor of the University of Tennessee, Knoxville, in 1991 and 1992, the Philips Chair Professor of the Technical University of Hamburg, Germany, a visiting professor at Leeds Polytechnic University, UK, and a visiting professor of Pohang University of Science and Technology, Korea. He is also Honorary Professor of many Chinese universities. Prof. Liu is a Fellow of IEEE since 1998.

Prof. Liu has lead various research projects on gyrotrons, free electron lasers, and plasma electronics since 1964. More recently, he has been the principal investigator of the National Key Research Project on "Basic research of microwave plasmas and their applications" funded by National Science Foundation of China. Prof. Liu is presently a Distinguished Visiting Professor at Old Dominion University and the College of William and Mary, working in the field of microhollow cathode discharges, microwave plasma excited excimer lasers, and electromagnetic field effects on biological cells.

Special Issue Papers

1. **MS-PP-18**
   Biological Applications of Large Electric Fields: Some History and Fundamentals (*Invited Paper*)
   Charles Polk

2. **MS-PP-17**
   Thermal and Nonthermal Mechanisms of Interaction of Radiofrequency Energy with Biological Systems (*Invited Paper)*
   K. Foster

3. **MS-PP-13**
   Electroporation of Cells and Tissues (*Invited Paper)*
   J. Weaver

4. **MS-PP-16**
   Electromanipulation of Mammalian Cells: Fundamentals and Applications *(Invited Paper)*
   U. Zimmermann, U. Friedrich, H. Mussauer, P. Gessner, K. Hamel, and V. Sukhorukov

5. **MS-PP-08**
   Medical Applications of Electroporation (*Invited Paper)*
   S. Dev, D. Rabussay, G. Widera, and G. Hofmann

11. MS-PP-11
   Electroporation and Increase of Cytotoxicity of Anticancer Drugs due to Low Intensity Transient Pulses
   C. Liu, B. Wang, Z. Wang, and H. Zhang

6. **MS-PP-22**
   A Review of Short Pulse Generator Technology (*Invited Paper)*
   M. Kristiansen, and J. Mankowski

7. MS-PP-05
   Development of Electrophysical Installations for Medical and Technological Applications in Efremov Institute
   V.A. Burtsev, V.A. Glukhikh, G.Sh. Manukian, and B.P. Yatsenko

8. MS-PP-10

A Fast Pulsed Power Source for Treatment of Conducting Liquids

E.J.M. van Heesch, A.J.M. Pemen, P.A.H.J. Huijbrechts, P.C.T. van der Laan, K.J. Ptasinski, G.J. Zanstra, and P. de Jong

9. MS-PP-07

Inactivation of Pathogenic and Spoilage Microorganisms in Liquids Using Pulsed Electric Fields

S.J. MacGregor, O. Farish, R. Fouracre, N.J. Rowan, and J.G. Anderson

10. MS-PP-14

Inactivation of Bacillus Stearothermophilus by Pulsed Electric Fields

S. Katsuki, T. Majima, K. Nagata, I. Lisitsyn, H. Akiyama, M. Furuta, T. Hayashi, K. Takahashi, and S. Wirkner

12. MS-PP-09

Experimental Investigation of the Action of Pulsed Electric Discharges in Liquids on Biological Objects

N.M. Efremov, B.Yu. Adamiak, V.I. Blochin, S.Ja. Dadashev, K.I. Dmitriev, V.N. Semjonov, V.F. Levashov, and V.F. Jusbashev

13. MS-PP-23

Biofouling Prevention with Pulsed Electric Fields

A. Ghazala and K.H. Schoenbach

14. MS-TF-01

Pulsed Microwave Induced Bioeffects *(Invited Paper)*

J.L. Kiel, J.E. Parker, P.J. Morales, J.L. Alls, P.A. Mason, R.L. Seaman, S.P. Mathur, and E.A. Holwitt

15. MS-TF-06

Low Intensity Millimeter Waves as a Novel Therapeutic Modality *(Invited Paper)*

A. Pakhomov and M. Murphy

16. MS-TF-02

Coupling of Low Frequency Electromagnetic Fields to Activate DNA: Stimulation of the Cellular Stress Response *(Invited Paper)*

M. Blank and R. Goodman

17. MS-PP-21

Structural Changes in Cell Membranes after Ionizing Electromagnetic Field Exposure *(Invited Paper)*

J. Hannig and R.C. Lee

18. MS-PP-15

Inactivation of Food-Borne Enteropathogenic Bacteria and Spoilage Fungi Using Pulsed Light

J. Anderson, N. Rowan, S. MacGregor, R. Fouracre, and O. Farish

19. MS-PP-19

The Development of Photosensitized Pulsed and Continuous Ultraviolet Decontamination Techniques for Surfaces and Solutions

K. McDonald, R. Curry, T. Clevenger, B. Brazos, and K. Unklesbay

20. MS-PP-20

The Effect of High Dose Rate X-Rays on E. Coli O157:H7 in Ground Beef

R. Curry, K. Unklesbay, N. Unklesbay, T. Clevenger, B. Brazos, G. Mesyats, and A. Filatov

21. MS-IG-12

Generation of Large Volume, Atmospheric Pressure, Non-Equilibrium Plasmas *(Invited Paper)*

E.E. Kunhardt

22. MS-IG-03

An Overview of Research Using the One Atmosphere Uniform Glow Discharge (OAUGDP) for Sterilization of Surfaces and Materials *(Invited Paper)*

T.C. Montie, K. Kelly-Wintenberg, and J. Reece Roth

23. MS-IG-07

Biological Decontamination by Non-Thermal Plasmas

M. Laroussi, I. Alexeff, E. Garate, and W. Kang

24. MS-IG-11

Action of the Selfsustained Glow Discharge in Air of Atmospheric Pressure on Biological Objects

N.M. Efremov, B.Yu. Adamiak, V.I. Blochin, S.Ja. Dadashev, K.I. Dmitriev, V.N. Semjonov, V.F. Levashov, and V.F. Jusbashev

25. MS-IG-14
The Primary Physicochemical Mechanism of Beneficial Biological/Medical Effects of Negative Air Ions
M.N. Kondrashova, E.V. Grigorenko, A.N. Tikhonov, T.V. Sirota, A.V. Temnov, and V.P. Tikhonov

26. MS-IG-04
Air Filter Sterilization Using a One Atmosphere Uniform Glow Discharge Plasma (the Volfilter)
K. Kelly-Wintenberg, D.M. Sherman, P.P.Y. Tsai, R.B. Gadri, F. Karakaya, Z. Chen, J. Reece Roth, and T.C. Montie

27. MS-IG-01
Bacterial Decontamination Using Ambient Pressure Nonthermal Discharges *(Invited Paper)*
J.G. Birmingham and D.J. Hammerstrom

28. MS-IG-13
Rapid Decontamination of Large Surface Area
L.C. Farrar, J.C. Dickens, E.A. O'Hair, and J.A. Fralick

29. MS-IG-02
A Remote Exposure Reactor (RER) for Plasma Processing and Sterilization by Plasma Active Species at One Atmosphere
J. Reece Roth, D.M. Sherman, R.B. Gadri, F. Karakaya, A. Chen, T.C. Montie, K. Kelly-Wintenberg, and P.P.Y. Tsai

30. MS-IG-08
Production of Nitric Monoxide Using Pulsed Discharges for a Medical Application
T. Namihira, S. Tsukamoto, D. Wang, S. Katsuki, H. Akiyama, K. Okamoto, and R. Hackam

31. MS-IG-10
Overview of the Application of Nanosecond Electron Beams for Radiochemical Sterilization
Yu.A. Kotov, S.Yu. Sokovnin, M.E. Balezin, Y.S. Nizhechik, and L.L. Ananicheva

32. MS-IG-15

Ion Beam for Application in Genetic Modification *(Invited Paper)*

Yu Zengliang

33. MS-IG-06

Effect of Air Plasma of Glowing Discharge on Grain Crops Seed

A.E. Dubinov, E.M. Lazarenko, and V.D. Selemir

ElectroMed99

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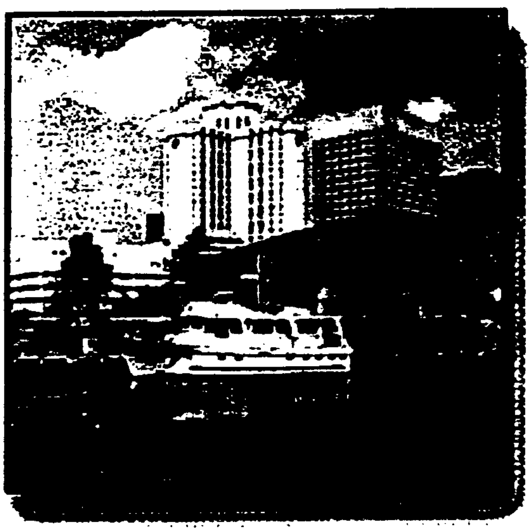

April 12 - 14, 1999
Waterside Marriott
Norfolk, VA

Sponsored by:

U.S. Air Force Office of Scientific Research (AFOSR)
National Science Foundation (NSF)
Institute of Electrical and Electronics Engineers (IEEE)
Bioelectromagnetics Society (BEMS)
Old Dominion University (ODU)
College of William and Mary (CW&M)
Eastern Virginia Medical School (EVMS)

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	Shenggang Liu University of Electronic Science and Technology of China

PROGRAM COMMITTEE

Hidenori Akiyama	Kumamoto,U. Japan
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Stephen Beebe	Eastern Viginia Medical School
Klaus Frank	U. Erlangen, Germany
Ben Greenbaum	U. of Wisconsin
S. Liu	U. Electronic Science and Technology of China
D. Manos	College of William and Mary
C. Polk	U. of Rhode Island
E. Postow	National Institutes of Health
K. Schoenbach	Old Dominion University

ElectroMed99

AGENDA

Sunday, April 11, 1999

6.00 p.m. Registration and Reception

Monday, April 12, 1999

7.00 am *Continental Breakfast*

8.15 am Introduction
K.H. Schoenbach

8.30 am Opening Remarks
The Honorable Owen B. Pickett, Member of the U.S. House of Representatives

Session I: Electromagnetic Fields: Sources and Biological Effects

Chair: R. Barker

8.50 am C. Polk (University of Rhode Island)
Large Electric Fields: Boon or Bane - Some History and Fundamental Concepts

9.30 am J. Weaver (MIT/Harvard)
Electroporation of Cells and Tissues

10.00 am ***Break***

10.30 am M. Kristiansen (Texas Tech University)
Pulsed Electrical Power Systems

11.00 am A. Pakhomov and M. Murphy (AFRL, Brooks AFB)
Low-Intensity Millimeter Waves as a Novel Therapeutic Modality

11.30 am E. Schamiloglu (University of New Mexico)
Pulsed Microwave and Millimeter-Wave Sources

12.00 ***Lunch***

1.30 pm M. Blank (Columbia University)
Coupling of AC Electric Fields to Cellular Processes

2.00 pm K. Foster (University of Pennsylvania)
RF Interactions with Biological Systems Considered in the Time Domain

2.30 pm U. Zimmermann and V. Sukhorukov (University of Wuerzburg, Germany)
Electromanipulation of Cells

2.50 pm Break

Session II: Ionized Gases: Sources and Applications

Chair: R. Barker

3.20 pm E. Kunhardt (Stevens Institute of Technology)
Generation and Characteristics of Nonthermal Atmospheric Pressure Plasmas

3.50 pm T. Montie, K. Kelly-Wintenberg, and J. Reece Roth (University of Tennessee)
An Overview of Research Using a One-Atmosphere Glow Discharge Plasma for Sterilization of Surfaces and Materials

4.20 pm J. Birmingham (MesoSystems Technology, Inc.)
Bacterial Decontamination Using High Pressure Nonthermal Discharges

4.50 pm P. Netzer (National Naval Medical Center)
Sterilization Methods in Healthcare

7.00 p.m. Dinner Cruise on the Schooner "American Rover"

Tuesday, April 13, 1999

7.30 am Continental Breakfast

Session III: Electromagnetic Fields: Medical Applications

Chair: Shenggang Liu

8.30 am J. Leon (University of Montreal)
Modeling and Experimental Studies on Ventricular Fibrillation and Defibrillation

9.00 am R.C. Lee, J. Hannig, and M. Bier (University of Chicago)
Tissue Manifestations of Electric Force Injury in Electric Shock

9.30 am G. Hofmann (Genetronics, Inc.)
Medical Applications of Electroporation

10.00 am W.R. Panje, M.P. Hier, and E. Harrell (Rush-Presbyterian-St. Luke's Medical Center, Chicago, IL)
Electroporation Therapy of Head and Neck Cancer

10.30 am *Break*

Session IV: Electromagnetic Fields/Particle Beams: Biological Effects and Applications

Chair: Shenggang Liu

11.00 am J. Kiel, J. E. Parker, J. L. Alls, and P. J. Morales (AFRL, Brooks AFB)
Pulsed Microwave Induced Bioeffects

11.30 K.H. Schoenbach (Old Dominion University), S. Beebe, and S. Buescher (Eastern Virginia Medical School)
Biological Effects of High Power, Microsecond and Submicrosecond Electrical Pulses

12.00 am *Lunch*

1.30 pm P. Dunne (US Army Natick RD&E Center)
Pulsed Electric Fields for Pasteurization of Food

2.00 pm Yu Zengliang, Wu Lifang, and Li Hong (Chinese Academy of Science)
Ion Beam Application for Genetic Modification

2.30 pm – 5.00 pm ***Poster Session***

6.00 p.m. Banquet in the Huber Court of the Chrysler Museum

Wednesday, April 14, 1999

8.00 am *Continental Breakfast*

9.00 am ***Group Discussions in Breakout Rooms***

1. Biological Effects of Pulsed Electric Fields
Chair: J. Dunn (ALP, Chicago)

2. Biological Effects of Micro- and Millimeter-Waves
Chair: NN

3. Medical Applications of Bioelectric Effects
Chair: R.C. Lee (University of Chicago)

4. Ionized Gases for Biological Decontamination
Chair: I. Alexeff (University of Tennessee)

1.30 pm ***Panel Discussion***

Chair: R. Barker (AFOSR)

Chairs of Discussion Groups:
- I. Alexeff (U. Tennessee)
- J. Dunn (ALP, Chicago)
- R. Lee (U. Chicago)
- NN

P. Dunne (US Army)
R. Ellis (USDA)
L. Goldberg (NSF)
S. Liu (UESTC)
E. Postow (NIH)
D. Quass (EPRI)
G. Roy (ONR)

ElectroMed99

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Symposium Record
Abstracts

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K. Schoenbach	Old Dominion University

TRAVEL GRANTS FOR GRADUATE STUDENTS

The National Science Foundation (NSF) has provided travel support for graduate students and young postdoctoral scientists to attend the symposium. Applicants for student travel grants were requested to send a short CV and one reference letter to the conference organizer. Preference was given to those students who are authors or co-authors of an already submitted poster paper, or have submitted an abstract for the poster session together with their application. The award selection was made by the Organizing Committee. Eight students and postdoctoral scientists have received travel grants to the symposium.

SOCIAL PROGRAM

A variety of social events are being planned for the duration of the Symposium. The program will include a Welcoming Reception held the evening of April 11th at the Marriott Hotel.

The Symposium Banquet will be held on Tuesday evening at the Chrysler Museum. The Museum houses a collection of over 30,000 objects spanning nearly 4,000 years of Art History. Highlights include an internationally famous glass collection that includes holdings of blown glass made by Tiffany Studios and outstanding Tiffany lamps. There will be entertainment presented by the Hampton Roads Chamber Players, a group of young musicians from the Governor's School of the Arts, and a group of musicians from Old Dominion University. Transportation will be provided to and from the Museum.

Additionally, a cruise with dinner on the American Rover, a three-mast schooner will be on Monday evening. Registration for this event was optional and required early registration. The American Rover is within walking distance of the Marriott Hotel.

Special Issue of the IEEE Transactions on Plasma Science

"Nonthermal Medical/Biological Treatments Using Electromagnetic Fields and Ionized Gases"

(Scheduled for February 2000)

Recent advances in the generation of ultrashort high power electrical pulses have opened new venues in the field of bioelectrics. Electrical pulses of duration less than a billionth of a second but at voltages exceeding ten thousand volts allow one to explore and to utilize electrical interactions with biological cells without significant heating of the tissue. The high frequency components in the ultrashort pulses have been shown to provide an effective pathway to the interior of the cells. Pulsed, high power microwave and millimeter wave sources allow one to similarly explore and utilize nonlinear processes on the *molecular* level, with the potential to some day selectively modify individual molecular structures, such as DNA.

Equally exciting is the growing field of research into the application of plasmas for chemical and biological sterilization and decontamination. A number of industrial and university research groups have already demonstrated the remarkable ability of relatively cold ionized gases to rapidly kill bacteria cells while avoiding the excessive heat and/or harsh chemicals associated with current conventional sterilization techniques. This new approach poses major advantages for both defense and commercial medical applications.

On April 12-14 1999, an international symposium will be held in Norfolk, VA, to carefully consider the tremendous opportunities growing in these new areas. In particular, a special effort will be made to use this forum to introduce M.D.s and biologists to these non-chemical treatments. Detailed information about the symposium may be found on the website www.ece.odu.edu/~emed99

The intent of the *TPS* Special Issue is to provide a wider forum for this topic and to assemble papers addressing both the fundamental and applied aspects of nonthermal electromagnetic and plasma effects on biological cells. Contributions are solicited in, but not restricted to, the following areas:

- *Electroporation of Cells and Tissues*
- *Medical Applications of Electroporation*
- *Pulsed Electric Fields for Debacterialization*
- *Interaction of High Frequency Electromagnetic Fields with Biological Systems*
- *Pulsed Microwave Induced Bioeffects*
- *Biological Effects of Millimeter Waves*
- *Air Plasma Sterilization of Surfaces and Materials*
- *Bacterial Decontamination Using High Pressure Nonthermal Discharges*

Please submit three copies of the manuscript, original figures, and a signed IEEE copyright form to one of the three guest editors whose addresses appear below. The deadline for submitting manuscripts is **May 1, 1999.** To ensure maximum speed in correspondence, please include telephone and FAX numbers and email address of the corresponding author. Further detailed instructions for authors may be found on the inside back cover of the *IEEE Transactions on Plasma Science,* and on the web*: www.IEEE.org/pubs/authors.html.*

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Bacterial Decontamination Using High Pressure Nonthermal Discharges
J. Birmingham, MesoSystems Technology, Inc.

Sterilization Methods in Healthcare
P. Netzer, National Naval Medical Center

Modeling and Experimental Studies on Ventricular Fibrillation and Defibrillation
J. Leon, University of Montreal

LARGE ELECTRIC FIELDS: BOON OR BANE - SOME HISTORY AND FUNDAMENTAL CONCEPTS

Charles Polk
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Scientific analysis of electricity in biology began with the work of Luigi Galvani near the end of the 18th century. Using a bimetallic arch (zinc and copper) he was able to produce muscular contractions in a frog leg. Galvani, who was a practicing physician, attributed the effect to "animal electricity existing in the body". This started a controversy with Alessandro Volta, professor of physics in Pavea, who repeated Galvani's experiment and discovered that the electric potential required the contact between the two dissimilar metals. Another Italian, Carlo Matteuci (1811-1865) was then the first to measure a true biogenic impulse in frog muscle. Experimental exploration of bioelectric phenomena proceeded rather rapidly after about 1840 in France, Germany and England. In 1887 August Waller recorded the first electrocardiogram and even earlier, in 1872, Thomas Green in the U.S. resuscitated five of seven complications of chloroform anesthesia. He used a 300 volt battery and thus pioneered the first application of high voltage in human medicine. Closed chest ventricular pacing in patients with atrioventricular block was introduced in the US by Zoll in *1952* using 2 ms, 150 V pulses at rates between 30 and 180 per minute. Later, in the 1950's commercial implantable pacemakers became available. Very large electric fields, up to 300 V/m can usually restore the normal heartbeat in ventricular fibrillation if applied quickly. Ventricular fibrillation is one of the leading causes of death in the Western world with about 1200 cases each day. The first defibrillator was produced by William Kouwenhoven, an electrical engineer, in 1930. Many refinements were made since that time and a DC defibrillator developed in 1962 by Bernard Lawn, a cardiologist at the Harvard Medical School, is still used today. However, ventricular fibrillation and methods for stopping it are still a very active research area. An important reason for this is that transchest defibrillation energy, using present methods, is 200-360 Joule with currents of 2-3 amperes. These currents frequently produce burn injuries at the points of highest current density, generally close to the electrodes. A burn, of course, is a thermal effect which occurs here in an application that only requires non-thermal stimulation.

The question of what is a thermal effect is central to the present conference. As in the defibrillator example, some non-thermal effects are occasionally accompanied by thermal effects; at other times some effects which are thought to be non-thermal turn out to be thermal - such as "microwave hearing". I also suspect that sometimes effects which are attributed to a small temperature increase are either due to temperature cycling, displacement of ions at a particularly critical location, conformational change of protein molecules, or a combination of all of these involving resonant absorption of energy at the right frequency and dimension of the target structure. Provided that the material subjected to an electric field (E) follows Ohm's law - that is a linear relation between current density and electrical conductivity (σ), it can be shown that the time rate of change of temperature (T) is given by $(\delta T/\delta t) = (\sigma E^2)I(c\rho)$, where c is the specific heat capacity of the material and p its density. However, as soon as we deal with a time varying B, even the application of this simple relation, that is valid only when the material behaves linearly, can become very complex. We must then realize that, depending on material properties and on frequency and polarization of S, reflection of E at material boundaries takes place, penetration depth varies and absorption of energy depends on size of the exposed object in terms of wavelength. Some of these effects will be discussed, as will be the definitions of SAR (specific absorption rate), SA (specific absorption) and the significance of power spectral density for unidirectional pulses, as well as for pulse modulated sinusoidal signals.

PULSED ELECTRICAL POWER SYSTEMS

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The basic pulsed power concepts and the most common pulsed power circuits are reviewed briefly. Several novel, short pulse devices are described in some more detail. Most of these devices are developed in Russia and are now commercially available through various US representatives. These devices can produce output voltages exceeding 100 kV (1 MV for single pulse) into 50 Ω with pulse widths as short as 150 ps and repetition rates of several thousand pulses per second. They are compact and reliable and several of them have been used extensively for various research projects in our laboratory.

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PULSED MICROWAVE AND MILLIMETER-WAVE SOURCES

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Microwaves are electromagnetic radiation of frequencies spanning the range from about 500 MHz (500 million cycles per second) to 300 GHz (300 billion cycles per second); this corresponds to a wavelength range of 60 cm to 1 mm. The present microwave spectrum bands designated by the Institute of Electrical and Electronic Engineers (IEEE) are *L* (1-2 GHz), *S* (2-4 GHz), *C* (4-8 GHz), *X* (8-12 GHz), *Ku* (12-18 GHz), *K* (18-27 GHz), *Ka* (27-40 GHz), and finally the millimeter (40-300 GHz). Therefore, when describing "microwaves," one typically includes millimeter waves as well.

The earliest source of microwaves was a spark gap pioneered by Heinrich Hertz in 1887. The development of sources capable of generating microwave radiation with considerable power levels can be attributed to the development of radar, which started after World War I, but grew in intensity during World War II. The earliest of these sources were variants of the conventional vacuum tube, such as the German Barkhausen-Kurz electric valve, first proposed in 1920. A novel approach was proposed in 1921 by Albert W. Hull at the General Electric Research Laboratory. This "magnetron" used a magnetic field to insulate the circular flow of electrons in the device. Further development of the magnetron is credited to Randall and Boots in England in 1939, and this device proved essential to the defense of England, as well as a fixture in most homes today. The 1930s also saw the birth of linear electron beam-driven microwave sources, such as the backward wave oscillator, traveling wave tube amplifier, and the klystron.

The thrust since the 1940's has been to generate high power levels at increasingly higher frequencies. A measure of this is the "quality factor" Pf^2, the product of the peak microwave power and the square of its frequency. The conventional devices, such as those described in the previous paragraph, made three orders of magnitude progress in the quality factor between 1940 and about 1970, but thereafter only minor improvements were made, primarily by klystrons. At about 1970 a new technology (pulsed power) was employed to generate intense relativistic electron beam-driven cousins of the conventional devices, thereby yielding an additional three orders of magnitude increase in the quality factor between 1970 and 1990.

This tutorial will present an introduction to microwaves, and an overview of the state-of-the-art in sources capable of providing high power levels across the spectrum. An emphasis will be placed on pulsed sources, and particular attention will be paid to those sources that appear promising to medical applications.

RF INTERACTIONS WITH BIOLOGICAL SYSTEMS CONSIDERED IN THE TIME DOMAIN

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Most of the discussion of potential biological effects of electromagnetic fields is done in the frequency domain, because of the narrow-band nature of most exposure sources. The advent of technologies employing wideband or ultrashort RF pulses suggests the need for analysis in the time domain also. This problem is analogous to the century-old problem of determining the threshold for shock from pulses of electric current, and concepts of chronaxie and rheobase, deriving from that work, are still useful. I review some of the many mechanisms by which RF energy has been shown to interact with biological systems. Apart from thermal mechanisms, most involve, ultimately, electrically induced forces on biological structures. These mechanisms can be classified according to a series which, in order of decreasing strength, is field-charge interactions, field-permanent dipole interactions, and field-induced dipole interactions. In each case, the mechanism is characterized by a time constant (corresponding to chronaxie) and a threshold stimulus (rheobase) needed to produce a detectable effect. In addition, the coupling between external fields and cellular structures is characterized by a series of time constants for the different polarization mechanisms. I present order-of-magnitude estimates for the relevant time constants and thresholds for producing established biological effects, in comparison with potential levels of human exposure to fields produced by ultrawideband technologies.

GENERATION AND CHARACTERISTICS OF NONTHERMAL ATMOSPHERIC PRESSURE PLASMAS

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BACTERIAL DECONTAMINATION USING HIGH PRESSURE NONTHERMAL DISCHARGES

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A brief history is presented concerning the application of plasmas to the destruction of biological and chemical contaminants. Special mention is paid to the effects of dielectric packing materials on the stability and effectiveness of barrier discharges. The observations of the effectiveness of packed barrier discharge plasmas on chemical and biological samples, first made in U.S. Army laboratories in the 1970s and 1980s, recently have been repeated by MesoSystems Technology, Inc. and others by invitation from the U.S. military. Our observation has been that biological cells and spores are killed in seconds, a rate that significantly exceeds the kill rate obtained by heat alone. The kill rate of chemical decontamination using the barrier discharge plasma is similar to that obtained using heat alone. Recent observations have been made concerning the effectiveness of short bursts of plasma in destroying spore walls. This observation is of great interest to those tasked with detection of pathogenic spores.

MODELING AND EXPERIMENTAL STUDIES ON VENTRICULAR FIBRILLATION AND DEFIBRILLATION.

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Sudden Cardiac Death kills over 200,000 north Americans each year. The only therapy is defibrillation using strong electrical shocks. Although extremely effective, there is still no clear understanding as to how the shock field manages to stop fibrillation, and return the heart to a normal rhythm. The ultimate goal of our work is to develop an understanding of the mechanisms underlying cardiac fibrillation and how it can be terminated using strong electrical shocks, with a view to designing more effective implantable devices.

We have chosen to attack the problem from three different angles:

1) Mathematical/computer modeling of the electrical activity in cardiac tissue.
2) Modeling of the interaction of the shock field with the cardiac electrical activity.
3) Experiments using voltage sensitive dyes to study the dynamics of fibrillation, and its termination.

In this talk I will outline the dynamics of fibrillation and show some modeling and experimental results of its initiation. I will then present modeling results on the effects of strong electrical fields on the cardiac electrical activity, and show how tissue inhomogeneities may play an important role in the defibrillation process.

MEDICAL APPLICATIONS OF ELECTROPORATION

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Short pulses of electric field can transiently enhance the permeability of cell membranes to transport exogenous molecules into the cytosol. This effect, generally called electroporation, became well known in the last decade and is now a standard tool in molecular biology laboratories for the transformation of cells. More recently, it became apparent that electroporation can also be applied to cells in tissue. Genetronics is pursuing therapeutic applications of electroporation and has identified several main areas of interest: Transdermal delivery of large molecules, *in vivo* and *ex vivo* gene therapy, electroporation mediated therapy of cancer (EPT), and delivery of drugs and genes to vessel walls with electroporation catheters (EC) for the treatment of cardiovascular diseases. Feasibility was proven in all of these. Examples of implementations will be presented.

The furthest developed application is EPT, which has proceeded successfully into clinical trials. EPT is the technique of injecting a local tumor with a low dose of a chemotherapeutic agent. This agent generally does not easily permeate the tumor cells. By applying pulsed electric fields to the tumor tissue in the presence of the agent, the tumor cells become permeable to the agent and will be destroyed after entry. A special treatment system, the MedPulser™, was developed with needle array electrode applicators to achieve high tumor response rates even in tumors which were recalcitrant to prior radiation- or chemotherapy. The results of clinical trials will be reported.

Some cardiovascular diseases such as restenosis, the reocclusion of arteries after angioplasty procedures, could possibly benefit from the prolonged presence of efficacious drugs or genes at the site of vessel injury. For this goal we developed several electroporation catheters which, by generating locally at the vessel wall electroporation fields in the presence of drugs or genes, allow the transport of these molecules into the cells lining the vessels. Delivery of Heparin with electroporation catheters and prolonged presence in the vessel wall of rabbits was demonstrated. A marker gene could also be delivered into rabbit arteries and expression observed over the length of the observation period of 2 weeks. Uptake of antisense oligos into the arterial walls of pigs was shown as well as the intracellular uptake of propidium iodide.

Electroporation was demonstrated to be an effective tool for the delivery of drugs and genes *in vivo*. Human pilot studies showed efficacy in treating several types of cancer and it can be expected that this technique will find its way into the clinic in the foreseeable future.

PULSED MICROWAVE INDUCED BIOEFFECTS

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Pulsed microwave radiation of frequencies ranging from 1.25 GHz to 9.53 GHz , with pulse widths of 1μs to 2 msec, repetition rates of 10 to 100 pps, and peak incident powers from 6 kW to 2 MW, were examined for physical, biological, and biochemical effects that differed from continuous wave radiation. Sound generation, pulsed luminescence (including visible and ultraviolet light emission) , and electrical discharge were the physical phenomena observed, in that order, as the peak power levels were increased. These phenomena depended on the presence of simple chemicals such as dissolved carbon dioxide (or bicarbonate) and hydrogen peroxide. They were enhanced by the presence of the organic semi-conductor polymer diazoluminomelanin (DALM). Both the synthetic and biosynthetic forms of the polymer enhanced the effects. When the DALM was nitrated, the effects were further enhanced. When anthrax or _E.coli_ (a genetically engineered form) bacteria were placed in growth media to stimulate biosynthesis of DALM, their microwave radiation sensitivity was enhanced. Furthermore, when anthrax spores were placed in flashing solutions of DALM in a high power pulsed microwave field, they lost their ability to grow on some special medium but showed enhanced growth on blood agar. This result indicated some loss of gene function or expression. To date, EMT-6 cells (from mouse mammary adenocarcinoma) and HeLa cells (from human carcinoma of the cervix) have been transfected with a nitrate reductase gene fragment that allows them to make DALM and show microwave sensitivity like that of the aforementioned bacteria. The nitration enhancement of DALM-(a poly-tyrosine derivative)-mediated responses indicates the possibility that nitrated tyrosine, found naturally in inflamed tissue, could mediate enhanced absorption of pulsed microwave radiation. These preliminary results suggest that pulsed microwave radiation could be directed toward pathological targets in tissues and organs while sparing normal tissue.

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PULSED ELECTRIC FIELDS FOR PASTEURIZATION OF FOOD

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High voltage pulsed electric field (PEF) technology is a promising innovation in nonthermal food processing. Application of intense high voltage pulsed electric fields apparently results in irreversible cell membrane breakdown in microorganisms in foods while causing little loss of food flavor and taste as compared to traditional heat pasteurization. Treatment by pulses of 1-5 µsec duration above a threshold minimum of 15 -20kV/cm average field strength is considered adequate to inactivate most vegetative cells. Criteria for determining the success of PEF as a food process will be discussed. Pasteurization is defined as the elimination of viable pathogenic organisms along with a reduction of common spoilage organisms; it is not true sterilization because bacterial spores and other latent microbial forms are not necessarily inactivated. An operational goal for PEF Pasteurization would be to achieve a reduction of 10^6 or 6 logs of vegetative bacterial populations most likely to be found in the chosen food material without reaching temperatures of common thermal pasteurization (63 C).

Effectiveness of PEF in injuring or killing microbes in foods does seem to depend on complexity and size of the target organism. Sensitivity to PEF treatment follows the approximate order: parasites> yeasts & molds> Gm(-) bacteria> Gm(+) bacteria. However, Gm(+) bacterial spores, yeast ascospores, parasitic oocysts and viruses are quite resistant to PEF. Extended PEF treatment at elevated temperatures may damage a substantial population of certain bacterial spores, but it is quite unlikely that PEF alone will ever reach the 12-log reduction of *Clostridium botulinum* spores demanded for commercial sterilization of low-acid foods.

For both practical and regulatory reasons, commercial attention in PEF processing is now concentrated in the acid food category for fruit juices and other products with pH of ≤ 4.2. The acid tolerant pathogenic *E. coli* 0157:H7 is in the PEF-sensitive Gm(-) category, so effective PEF pasteurization of fruit juices can be demonstrated. PEF treatment of the Gm(+) pathogen *Listeria monocytogenes* in neutral dairy products may be more difficult.

For the purpose of demonstrating potential extension of PEF processing to shelf-stable products, a set of acid and acidified food prototypes have been developed for testing at the U.S. Army Natick Soldier Center. Sample products include spaghetti sauce, orange juice and yogurt-based drinks or puddings. Benefits of PEF treatment compared to traditional thermal processes include better retention of color, flavor and nutrient content. However, shelflife may be limited by action of residual enzymes in the foods because most enzymes are quite resistant to the PEF treatment levels needed for microbial control.

Electrical factors affecting PEF treatment success include treatment temperature, field strength, duration of treatment, the number of pulses delivered and pulse shape. A comparison of square wave versus exponential decay pulses has been made for orange juice using a pilot plant 40kV/8kW pulse generator at Ohio State University. Results of total aerobic plate counts from tests done using the square waveform (4.2 log cycles) indicated that more than an additional half log cycle reduction was obtained as compared with that achieved with exponential decay pulses (3.6 log cycles) of similar energy.

Reference:

J.E. Dunn and J.S. Pearlman, "Methods and apparatus for extending the shelf life of fluid food products", US patent 4,695,472, 1987.